(19) Europäisches Patentamt
European Patent Office
Office européen des br vets

(11) Publication number : **0 590 919 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **93307654.9**

(22) Date of filing : **28.09.93**

(51) Int. Cl.[5] : **C07D 473/06,** C07D 473/08, C07D 473/12, A61K 31/52

(30) Priority : **28.09.92 JP 257834/92**

(43) Date of publication of application : **06.04.94 Bulletin 94/14**

(84) Designated Contracting States : **AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE**

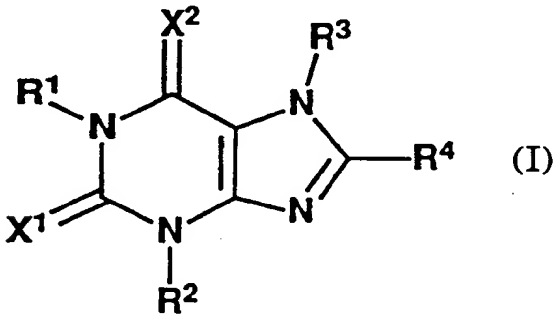
(71) Applicant : **KYOWA HAKKO KOGYO CO., LTD.**
6-1, Ohtemachi 1-chome
Chiyoda-ku Tokyo 100 (JP)

(72) Inventor : **Suzuki, Fumio, c/o Kyowa Hakko Kogyo Co., Ltd.**
6-1 Ohtemachi 1-chome, Chiyoda-ku
Tokyo (JP)
Inventor : **Shimada, Junichi, c/o Kyowa Hakko Kogyo Co., Ltd.**
6-1 Ohtemachi 1-chome, Chiyoda-ku
Tokyo (JP)
Inventor : **Koike, Nobuaki, c/o Kyowa Hakko Kogyo Co., Ltd.**
6-1 Ohtemachi 1-chome, Chiyoda-ku
Tokyo (JP)
Inventor : **Nakamura, Joji, c/o Kyowa Hakko Kogyo Co., Ltd.**
6-1 Ohtemachi 1-chome, Chiyoda-ku
Tokyo (JP)
Inventor : **Shiozaki, Shizuo, c/o Kyowa Hakk Kogyo Co., Ltd.**
6-1 Ohtemachi 1-chome, Chiyoda-ku
Tokyo (JP)
Inventor : **Ichikawa, Shunji, c/o Kyowa Hakko Kogyo Co., Ltd.**
6-1 Ohtemachi 1-chome, Chiyoda-ku
Tokyo (JP)
Inventor : **Nonaka, Hiromi, c/o Kyowa Hakko Kogyo Co., Ltd.**
6-1 Ohtemachi 1-chome, Chiyoda-ku
Tokyo (JP)

(74) Representative : **Lambert, Hugh Richmond et al**
D. YOUNG & CO., 21 New Fetter Lane
London EC4A 1DA (GB)

(54) Therapeutic agents for parkinson's disease.

(57) Disclosed as therapeutic agents for Parkinson's disease are xanthine derivatives of the formula (I) :



(I)

in which :

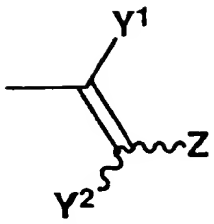
R^1 and R^2 each represent methyl or ethyl ;

R^3 represents hydrogen, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl or alkynyl ;

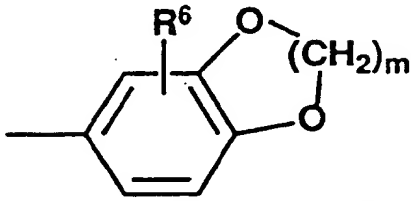
R^4 represents C_3-C_8 cycloalkyl ; a $-(CH_2)_n-R^5$ group where n is 0 or an integer of from 1 to 4, and R^5 represents phenyl, naphthyl or a h terocyclic group or a substituted phenyl, naphthyl or h terocyclic group containing from 1-4 substituents select d from C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, halogen, nitro, amino, mono- or di-(C_1-C_6) alkylamino, trifluoromethyl, benzyloxy, phenyl, phenoxy or C_1-C_6 alkoxy substituted by hydroxy, C_1-C_6 alkoxy, halogen, amino, azide, carboxy or (C_1-C_6 alkoxy)carbonyl ;

or a

EP 0 590 919 A1



group where Y^1 and Y^2 each represent hydrogen, halogen, or C_1-C_6 straight or branched chain alkyl ; and Z represents a



group in which R^6 represents hydrogen, hydroxy, C_1-C_6 straight or branched chain alkyl, C_1-C_6 straight or branched chain alkoxy, halogen, nitro, or amino, and m represents an integer of from 1 to 4 ; a phenyl, naphthyl or heterocyclic group or a substituted phenyl, naphthyl or heterocyclic group as defined under R^5 ;

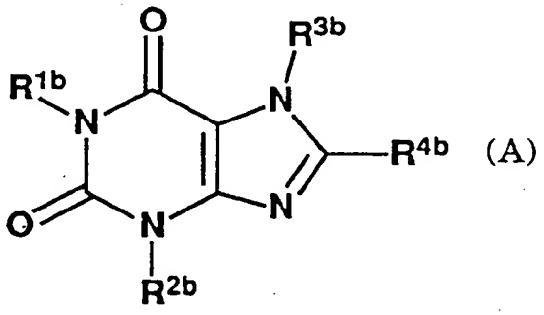
and X^1 and X^2 each represent O or S ;

or a pharmaceutically acceptable salt thereof.

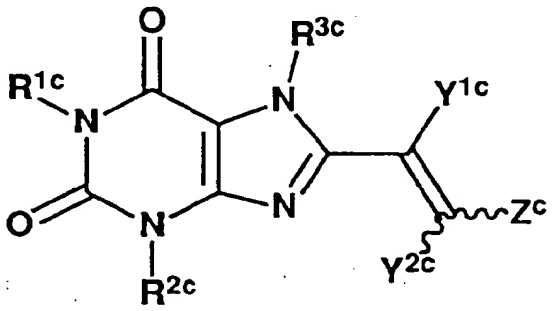
The present invention relates to therapeutic agents for the treatment of Parkinson's disease.

It is known that adenosine exhibits neurotransmitter depressing activity, bronchospasmic activity, and bone absorption promoting activity via an A_2 receptor. Therefore, adenosine A_2 receptor antagonists (hereinafter referred to as A_2-antagonists) are expected as therapeutic agents for various kinds of diseases through activated adenosine A_2 receptors, for example, therapeutic agents for Parkinson's disease, anti-dementia agents, anti-asthmatic agents, antidepressants, and therapeutic agents for osteoporosis.

Known compounds in this general field include compounds of formulae A and B:



(A)

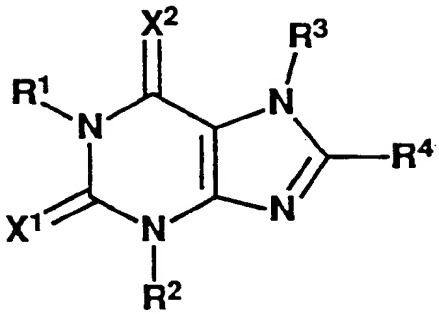


(B)

For example, it is known that adenosine antagonistic activity is found in compounds represented by Formula (A) in which R^{1b} and R^{2b} represent propyl, R^{3b} represents hydrogen, and R^{4b} represents substituted or unsubstituted phenyl, aromatic heterocyclic group, cycloalkyl, styryl, or phenylethyl [J. Med. Chem., 34, 1431 (1991)]. Further, U.S.P. 3,641,010 discloses, as brain stimulants, compounds represented by Formula (B) in which R^{1c} and R^{2c} independently represent methyl or ethyl, R^{3c} represents methyl, Y^{1c} and Y^{2c} represent hydrogen, and Z^c represents phenyl or 3,4,5-trimethoxyphenyl. WO92/06976 discloses, as compounds having an adenosine A_2 receptor antagonistic activity and therapeutic effects for asthma and osteoporosis, compounds represented by Formula (B) in which R^{1c} and R^{2c} independently represent hydrogen, propyl, butyl, or allyl, R^{3c} represents hydrogen or lower alkyl, Y^{1c} and Y^{2c} independently represent hydrogen or methyl, and Z^c represents phenyl, pyridyl, imidazolyl, furyl, or thienyl unsubstituted or substituted by 1 to 3 substituents such as lower alkyl, hydroxy, lower alkoxy, halogen, amino, and nitro. Furthermore, other compounds represented by Formula (B) are known. One is 8-styryl caffeine which is a compound of Formula (B) in which R^{1c}, R^{2c}, and R^{3c} represent methyl, Y^{1c} and Y^{2c} represent hydrogen, and Z^c represents phenyl [Chem. Ber. 119, 1525 (1986)]. Another is a compound of Formula (B) in which R^{1c}, R^{2c}, and R^{3c} represent methyl, Y^{1c} and Y^{2c} represent hydrogen, and Z^c represents pyridyl, quinolyl, or methoxy-substituted or unsubstituted benzothiazolyl [Chem. Abst. 60, 1741h (1964)]. However, there is no description with regard to the pharmacological activity of any of these compounds.

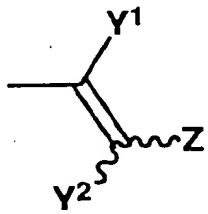
In accordance with the present invention, it has been found that xanthine derivatives of formula I have potent and selective adenosine A_2 receptor antagonistic activity and are therefore excellent propsective therapeutic reagents for the treatment of Parkinson's disease.

In one aspect, therefore, the present invention relates to the use of a xanthine derivative of Formula (I):

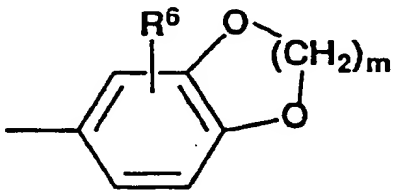


(I)

in which R^1 and R^2 represent independently methyl or ethyl;
R^3 represents independently hydrogen, lower alkyl, lower alkenyl, or lower alkynyl;
R^4 represents cycloalkyl, $-(CH_2)_n-R^5$ (in which R^5 represents substituted or unsubstituted aryl or a substituted or unsubstituted heterocyclic group; and n is an integer of 0 to 4), or



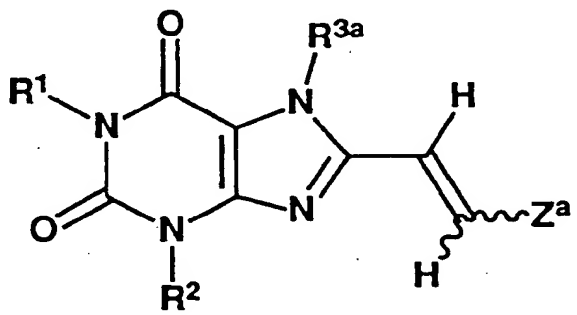
(in which Y^1 and Y^2 represent independently hydrogen, halogen, or lower alkyl; and Z represents substituted or unsubstituted aryl,



(in which R^6 represents hydrogen, hydroxy, lower alkyl, lower alkoxy, halogen, nitro, or amino; and m represents an integer of 1 to 3), or a substituted or unsubstituted heterocyclic group);
and X^1 and X^2 represent independently O or S, or pharmaceutically acceptable salts thereof for the preparation of pharmaceutical compositions useful for treating Parkinson's disease.

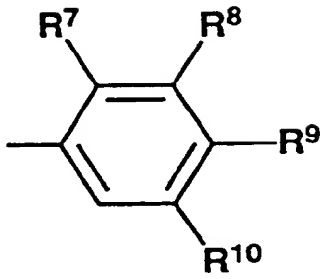
The compounds represented by Formula (I) are hereinafter referred to as Compounds (I), and the same applies to the compounds of other formula numbers.

The present invention also provides as novel compounds xanthine derivatives of Formula (I-A):

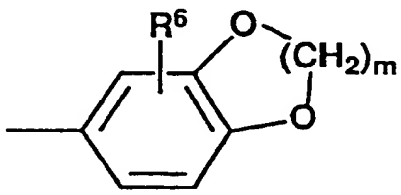


(I–A)

in which R^{3a} represents hydrogen or lower alkyl;
Z^a represents



(in which at least one of R^7, R^8, and R^9 represents lower alkyl or lower alkoxy and the others represent hydrogen; R^{10} represents hydrogen or lower alkyl) or



(in which R^6 and m have the same meanings as defined above), and their pharmaceutically acceptable salts.

In the definitions of the groups in Formula (I) and Formula (I-A), the lower alkyl and the lower alkyl moiety of the lower alkoxy mean a straight-chain or branched alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, and hexyl. The lower alkenyl means a straight-chain or branched alkenyl group having 2 to 6 carbon atoms, such as vinyl, allyl, methacryl, crotyl, 3-butenyl, 2-pentenyl, 4-pentenyl, 2-hexenyl, 5-hexenyl. The lower alkynyl means a straight-chain or branched alkynyl group having 2 to 6 carbon atoms, such as ethynyl, propargyl, 2-butynyl, 3-butynyl, 2-pentynyl, 4-pentynyl, 2-hexynyl, 5-hexynyl, 4-methyl-2-pentynyl. The aryl means phenyl or naphthyl. The cycloalkyl means a cycloalkyl group having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Examples of the heterocyclic group are furyl, thienyl, pyrrolyl, pyranyl, thiopyranyl, pyridyl, thiazolyl, imidazolyl, pyrimidyl, triazinyl, indolyl, quinolyl, purinyl, and benzothiazolyl. The halogen includes fluorine, chlorine, bromine, and iodine.

The substituted aryl and the substituted heterocyclic ring each has 1 to 4 independently-selected substituents. Examples of the substituents are lower alkyl, hydroxy, substituted or unsubstituted lower alkoxy, halogen, nitro, amino, lower alkylamino, di(lower alkyl)amino, trifluoromethyl, trifluoromethoxy, benzyloxy, phenyl, and phenoxy. The lower alkyl and the alkyl moiety of the lower alkoxy, lower alkylamino, and di(lower alkyl)amino have the same meaning as the lower alkyl defined above. The halogen has the same meaning as the halogen defined above. Examples of the substituent of the substituted lower alkoxy are hydroxy, lower-alkoxy, halogen, amino, azide, carboxy, and lower alkoxycarbonyl. The lower alkyl moiety of the lower alkoxy and lower alkoxycarbonyl has the same meaning as the lower alkyl defined above, and the halogen has the same meaning as the halogen defined above.

The above-mentioned pharmaceutically acceptable salts of Compounds (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, and amino acid addition salts.

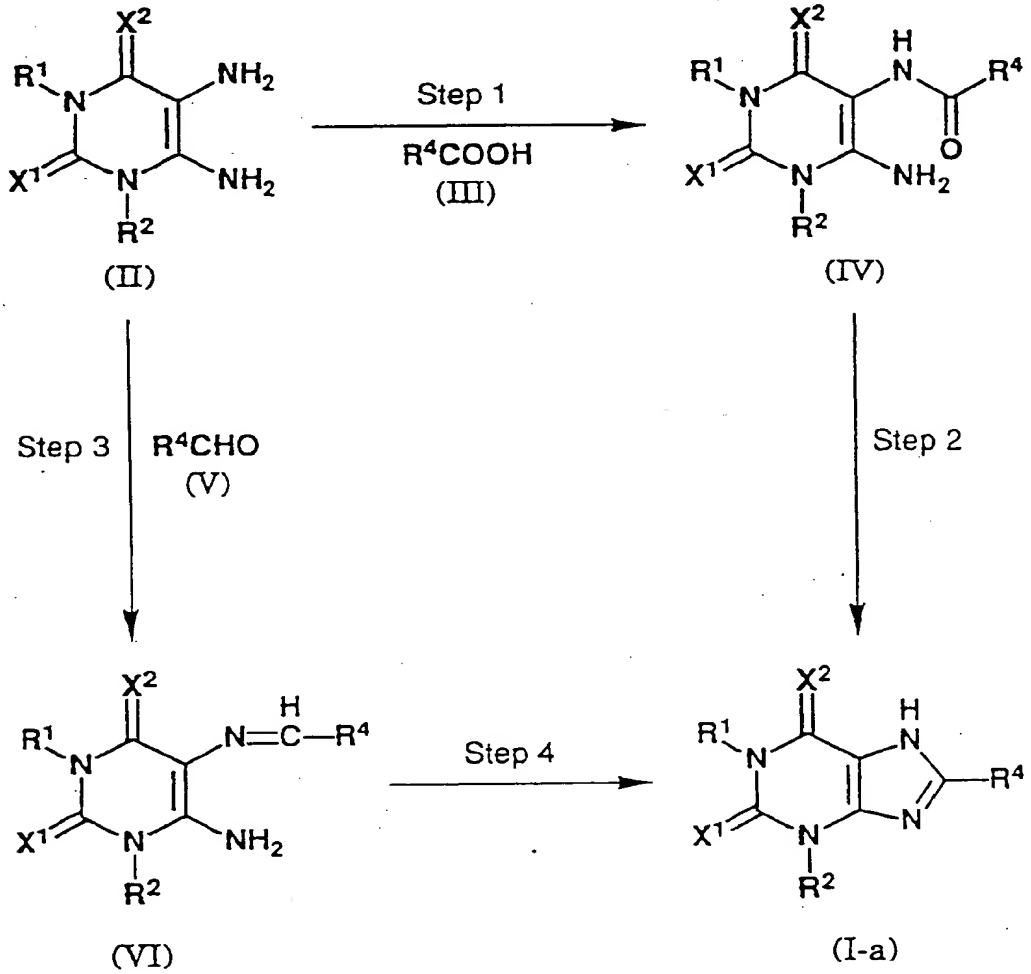
Examples of the pharmaceutically acceptable acid addition salts are inorganic acid addition salts such as hydrochloride, sulfate, and phosphate, and organic acid addition salts such as acetate, maleate, fumarate, tartrate, and citrate. Examples of the pharmaceutically acceptable metal salts are alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminium salt, and zinc salt. Examples of the pharmaceutically acceptable ammonium salts are ammonium salt and tetramethyl ammonium salt. Examples of the pharmaceutically acceptable organic amine addition salts are salts with morpholine and piperidine. Examples of the pharmaceutically acceptable amino acid addition salts are salts with lysine, glycine, and phenylalanine.

The processes for producing Compounds (I) are described below. Compounds (I) can also be produced

according to th methods described in, for example, U.S.P. 3,641,010; J. Med. Chem., 34, 1431 (1991); Chem. Ber., 119, 1525 (1986); and Chem. Abst., 60, 1741h (1964).

Process 1

Compound (I-a) [Compound (I) in which R^3 is hydrogen] can be prepared by the following reaction steps:



(In the formulae, R^1, R^2, R^4, X^1, and X^2 have the same meanings as defined above.)

(STEP 1)

A uracil derivative (II) obtained by a known method [for example, Japanese Published Unexamined Patent Application No. 42383/84; J. Med. Chem., 32, 1873 (1989)] is allowed to react with either a carboxylic acid (III) or a reactive derivative thereof to give Compound (IV). Examples of the reactive derivative of the carboxylic acid (III) are acid halides such as acid chloride and acid bromide, active esters such as p-nitrophenyl ester and N-oxysuccinimide, commercially available acid anhydrides, acid anhydrides produced by using carbodiimides such as 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, diisopropyl carbodiimide, and dicyclohexyl carbodiimide, and mixed acid anhydrides with monoethyl carbonate or monoisobutyl carbonate. If the carboxylic acid (III) is used, the reaction is completed in 10 minutes to 5 hours at 50 to 200°C without using a solvent.

If a reactive derivative of the carboxylic acid (III) is used, the reaction can be carried out according to a conventional method employed in peptide chemistry. That is, Compound (II) and a derivative of the carboxylic acid (III) are allowed to react in a solvent, preferably in the presence of an additiv or a base, to give Compound (IV). Examples of the solvent are halogenated hydrocarbons such as methylene chloride, chloroform, and ethy-

lene dichloride, ethers such as dioxane and tetrahydrofuran, dimethylformamide, dimethylsulfoxide, and water if necessary. An example of the additive is 1-hydroxybenzotriazole. Examples of the base are pyridine, triethylamine, 4-dimethylaminopyridine, and N-methylmorpholine. The reaction is completed in 0.5 to 24 hours at -80 to 50°C. The reactive derivative may be formed in the reaction system and then used without being isolated.

(STEP 2)

Compound (I-a) can be obtained by reaction of Compound (IV) carried out in any of the following manners: in the presence of a base (Method A); by treatment with a dehydrating agent (Method B); or by heating (Method C). In Method A, the reaction is carried out in a solvent in the presence of a base such as an alkali metal hydroxide (e.g. sodium hydroxide and potassium hydroxide). As the solvent, water, lower alcohols such as methanol and ethanol, ethers such as dioxane and tetrahydrofuran, dimethylformamide, dimethylsulfoxide, and the like may be used alone or in combination. The reaction is completed in 10 minutes to 6 hours at 0 to 180°C.

In Method B, the reaction is carried out in an inert solvent or in the absence of a solvent using a dehydrating agent such as a thionyl halide (e.g. thionyl chloride) and a phosphorus oxyhalide (e.g. phosphorus oxychloride). Examples of the inert solvent are halogenated hydrocarbons such as methylene chloride, chloroform and ethylene dichloride, dimethylformamide, and dimethylsulfoxide. The reaction is completed in 0.5 to 12 hours at 0 to 180°C.

In Method C, the reaction is carried out in a polar solvent such as dimethylformamide, dimethylsulfoxide, and Dowtherm A (Dow Chemicals). The reaction is completed in 10 minutes to 5 hours at 50 to 200°C.

(STEP 3)

Compound (II) is allowed to react with an aldehyde (V) to give a Schiff's base (VI). As a reaction solvent, mixtures of acetic acid and a lower alcohol such as methanol and ethanol may be used. The reaction is completed in 0.5 to 12 hours at -20 to 100°C.

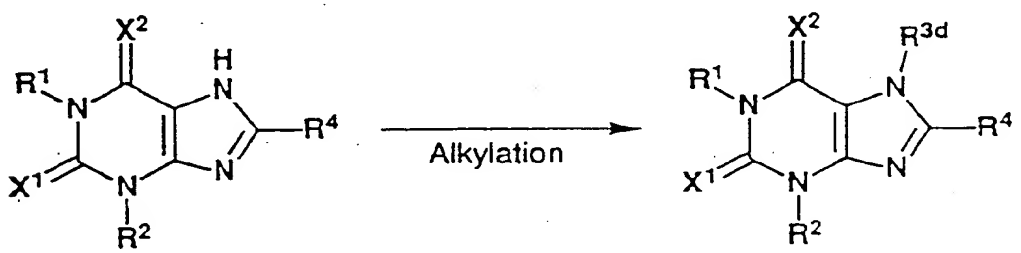
(STEP 4)

Compound (VI) is oxidatively cyclized in an inert solvent in the presence of an oxidizing agent to form Compound (I-a). Examples of the oxidizing agent are oxygen, ferric chloride, cerium (IV) ammonium nitrate, and diethylazodicarboxylate. Examples of the inert solvent are lower alcohols such as methanol and ethanol, halogenated hydrocarbons such as methylene chloride and chloroform, and aromatic hydrocarbons such as toluene, xylene, and nitrobenzene. The reaction is completed in 10 minutes to 12 hours at 0 to 180°C.

Process 2

Compound (I-b) [Compound (I) in which R^3 is a group other than hydrogen] can be prepared by the following reaction step.

Compound (I-b) is obtained from Compound (I-a) prepared by Process 1.



(I-a) (I-b)

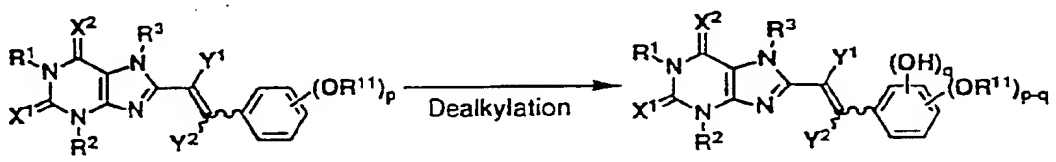
(In the formulae, R^{3d} represents a group other than hydrogen in the definition of R^3; and R^1, R^2, R^4, X^1, and X^2 have the same meanings as defined above.)

Compound (I-b) can be obtained by reaction of Compound (I-a) with an alkylating agent, in the presence of a base if necessary. Examples of the alkylating agent are alkyl halides such as methyl iodide, ethyl iodide, and allyl bromide, dialkyl sulfates such as dimethyl sulfate, sulfonic esters such as allyl p-tolenesulfonate and

methyl trifluoromethanesulfonate, and diazoalkanes such as diazomethane. Examples of the base are alkali metal carbonates such as sodium carbonate and potassium carbonate, alkali metal hydrides such as sodium hydride, and alkali metal alkoxides such as sodium methoxide and sodium ethoxide. As a reaction solvent, aromatic hydrocarbons such as toluene and xylene, ketones such as acetone and methyl ethyl ketone, dimethylformamide, dimethylsulfoxide, or the like may be used. The reaction is completed in 0.5 to 24 hours at 0 to 180°C.

Process 3

Compound (I-d) [Compound (I) in which Z is phenyl having hydroxy as substituent(s)] can be alternatively prepared by the following reaction step.



(I-c) (I-d)

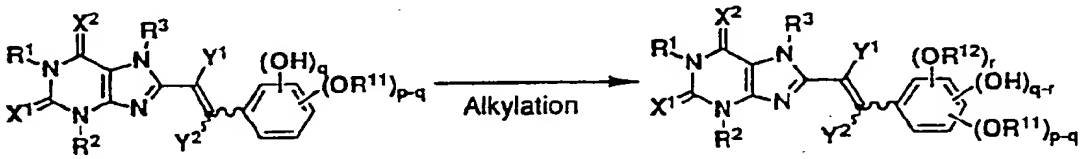
(In the formulae, R^{11} represents substituted or unsubstituted lower alkyl; p and q are integers of 1 to 4 and $p \geqq q$; and R^1, R^2, R^3, X^1, X^2, Y^1, and Y^2 have the same meanings as defined above.)

The substituted or unsubstituted lower alkyl in the definition of R^{11} has the same meaning as defined above.

Compound (I-d) can be obtained by reaction of Compound (I-c) [Compound (I) in which Z is phenyl having lower alkoxy as substituent(s)] obtained by Process 1 or Process 2 with a dealkylating agent. Examples of the suitable dealkylating agent are boron tribromide and the complex thereof with dimethyl disulfide, boron trichloride, iodotrimethylsilane, sodium ethanethiolate, sodium benzenethiolate, and hydrobromic acid. A reaction solvent is selected from aromatic hydrocarbons such as toluene and xylene, halogenated hydrocarbons such as methylene chloride, chloroform, and ethylene dichloride, dimethylformamide, acetic acid, etc. depending upon the kind of the dealkylating agent used. The reaction is completed in 10 minutes to 120 hours at -30 to 140°C.

Process 4

Compound (I-e) [Compound (I) in which Z is phenyl having lower alkoxy as substituent(s)] can be alternatively prepared by the following reaction step.



(I-d) (I-e)

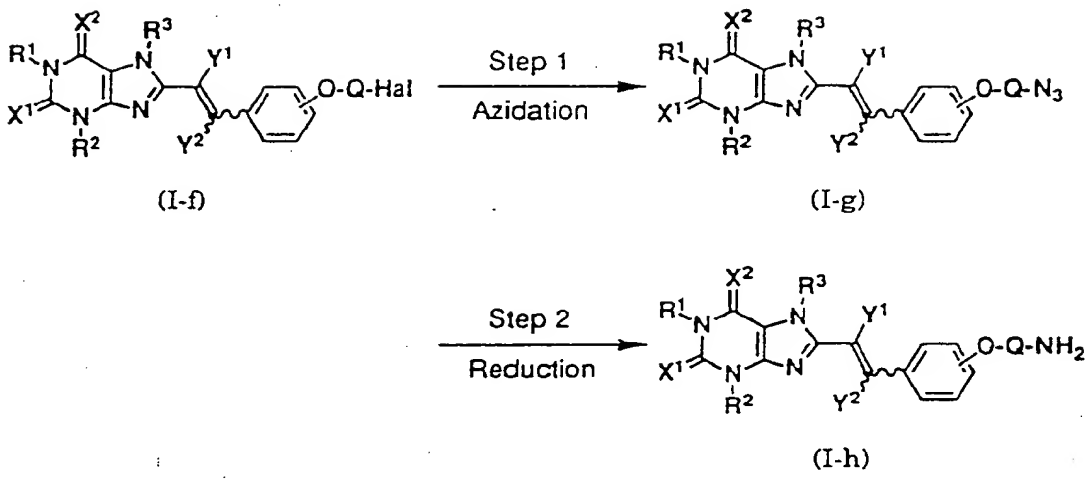
(In the formulae, R^{12} represents substituted or unsubstituted lower alkyl; r is an integer of 1 to 4 and $q \geqq r$; and R^1, R^2, R^3, R^{11}, X^1, X^2, Y^1, Y^2, p, and q have the same meanings as defined above.)

The substituted or unsubstituted lower alkyl in the definition of R^{12} has the same meaning as defined above.

Compound (I-e) can be obtained from Compound (I-d) according to the method of Process 2.

Process 5

Compound (I-h) [Compound (I) in which Z is phenyl having amino-substituted lower alkoxy as the substituent] can be alternatively prepared by the following reaction step.



(I-f) (I-g) (I-h)

(In the formulae, Q represents lower alkylene; Hal represents chlorine, bromine, or iodine; and R^1, R^2, R^3, X^1, X^2, Y^1, and Y^2 have the same meanings as defined above.)

The lower alkylene in the definition of Q means a straight-chain or branched alkylene group having 1 to 6 carbon atoms, such as methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 2-methylpropylene, pentylene, and hexylene.

(STEP 1)

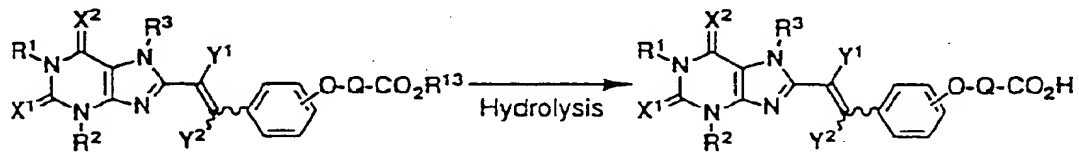
Compound (I-g) can be obtained by reaction of Compound (I-f) [Compound (I) in which Z is phenyl having chlorine, bromine, or iodine-substituted lower alkoxy as the substituent] obtained by Process 4 with 5 to 10 equivalents of sodium azide. As a reaction solvent, an inert solvent such as dimethylformamide may be used. The reaction is completed in 1 to 10 hours at 50 to 80°C.

(STEP 2)

Compound (I-h) can be obtained by treatment of Compound (I-g) in an inert solvent such as tetrahydrofuran and dioxane in the presence of 2 to 5 equivalents of a reducing agent such as triphenylphosphine, followed by addition of an excess of water and further treatment for 1 to 10 hours at 50°C to the boiling point of the solvent used.

Process 6

Compound (I-j) [Compound (I) in which Z is phenyl having carboxy-substituted lower alkoxy as the substituent] can be alternatively prepared by the following reaction step.



(I-i) (I-j)

(In the formulae, R^{13} represents lower alkyl; and R^1, R^2, R^3, Q, X^1, X^2, Y^1, and Y^2 have the same meanings as defined above.)

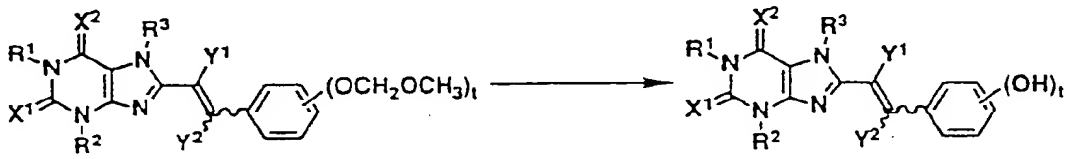
The lower alkyl in the definition of R^{13} has the same meaning as defined above.

Compound (I-j) can be obtained by hydrolysis of Compound (I-i) [Compound (I) in which Z is phenyl having lower alkoxycarbonyl-substituted lower alkoxy as the substituent] obtained by Process 4 in the presence of an alkali metal hydroxide such as sodium hydroxide and lithium hydroxide. As a reaction solvent, a mixture of water

and an ether such as dioxane and tetrahydrofuran, or a mixture of water and an alcohol such as methanol and ethanol may be used. The reaction is completed in 10 minutes to 12 hours at room temperature to the boiling point of the solvent used.

Process 7

Compound (I-m) [Compound (I) in which Z is phenyl having hydroxy as the substituent(s)] can be alternatively prepared by the following reaction step.



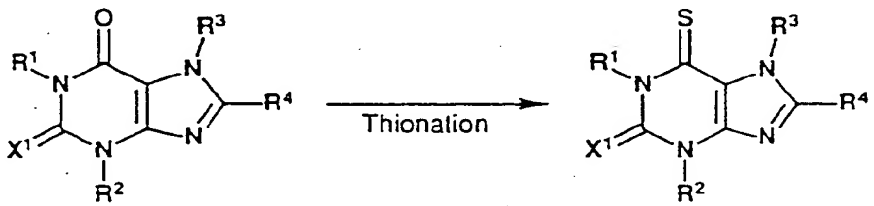
(I-k) (I-m)

(In the formulae, t is an integer of 1 to 4; and R^1, R^2, R^3, X^1, X^2, Y^1, and Y^2 have the same meanings as defined above.)

Compound (I-m) can be obtained by treatment of Compound (I-k) [Compound (I) in which Z is phenyl having methoxymethoxy as the substituent(s)] obtained by Process 1, Process 2, or Process 4 in the presence of hydrogen chloride gas, an aqueous solution of hydrochloric acid, or the like. As a reaction solvent, ethers such as dioxane and tetrahydrofuran, alcohols such as methanol and ethanol, or the like may be used. The reaction is completed in 1 to 20 hours at room temperature to the boiling point of the solvent used.

Process 8

Compound (I-o) [Compound (I) in which X^2 is S] can be alternatively prepared by the following reaction step.



(I-n) (I-o)

(In the formulae, R^1, R^2, R^3, R^4, and X^1 have the same meanings as defined above.)

Compound (I-o) can be obtained by reaction of Compound (I-n) [Compound (I) in which X^2 is O] obtained by Process 1 to Process 7 with a thionating agent. Examples of the thionating agent are phosphorus pentachloride and Leawsson's reagent. As a reaction solvent, pyridine, dimethylformamide, dioxane, tetrahydrofuran, or the like, preferably pyridine, may be used. The reaction is completed in 10 minutes to 36 hours at 50 to 180°C.

The desired compounds in the processes described above can be isolated and purified by purification methods conventionally used in organic synthetic chemistry, for example, filtration, extraction, washing, drying, concentration, recrystallization, and various kinds of chromatography.

In the case where a salt of Compound (I) is desired and it is produced in the form of the desired salt, it can be subjected to purification as such. In the case where Compound (I) is produced in the free state and its salt is desired, Compound (I) is dissolved or suspended in a suitable solvent, followed by addition of an acid or a base to form a salt.

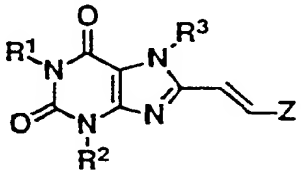
Some of Compounds (I) can exist in the form of geometrical isomers such as an (E)-isomer and a (Z)-isomer, and the present invention covers all possible isomers including the above-mentioned ones and mixtures thereof. In the case where separation between an (E)-isomer and a (Z)-isomer is desired, they can be isolated and purified by fractionation methods, for example, fractional crystallization, fractional precipitation, and frac-

tional dissolution.

Compounds (I) and pharmaceutically acceptable salts thereof may be in the form of adducts with water or various solvents, which can also be used as the therapeutic agents of the present invention.

Examples of Compounds (I) are shown in Table 1.

Table 1-1



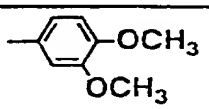
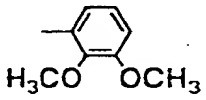
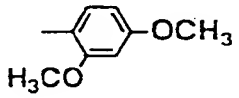
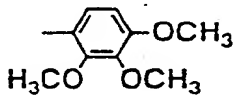
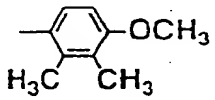
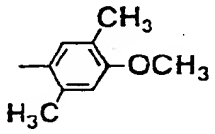
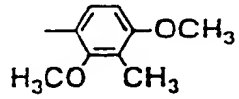
Compound	$-R^1$	$-R^2$	$-Z$	$-R^3$
1	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
2	"	"	"	$-CH_3$
3	"	"		$-H$
4	"	"	"	$-CH_3$
5	"	"		$-H$
6	"	"	"	$-CH_3$
7	"	"		$-H$
8	"	"	"	$-CH_3$
9	"	"		$-H$
10	"	"	"	$-CH_3$
11	"	"		$-H$
12	"	"	"	$-CH_3$
13	"	"		$-H$
14	"	"	"	$-CH_3$

Table 1-2

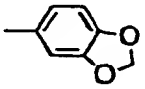
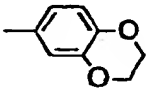
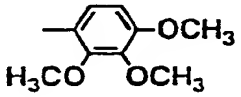
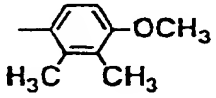
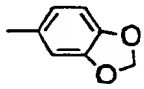
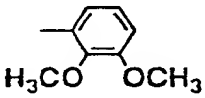
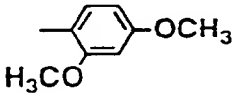
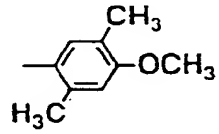
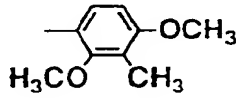
Compound	$-R^1$	$-R^2$	$-Z$	$-R^3$
15	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
16	"	"	"	$-CH_3$
17	"	"		$-H$
18	"	"	"	$-CH_3$
19	$-CH_3$	$-CH_3$		$-H$
20	"	"	"	$-CH_3$
21	"	"		$-H$
22	"	"	"	$-CH_3$
23	"	"		$-H$
24	"	"	"	$-CH_3$
25	"	"		$-H$
26	"	"	"	$-CH_3$
27	"	"		$-H$
28	"	"	"	$-CH_3$
29	"	"		$-H$
30	"	"	"	$-CH_3$
31	"	"		$-H$
32	"	"	"	$-CH_3$

Table 1-3

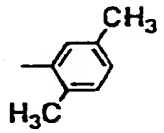
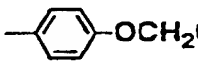
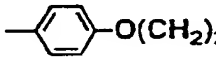
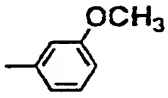
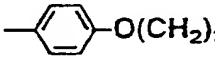
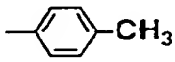
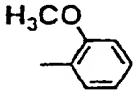
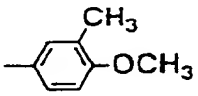
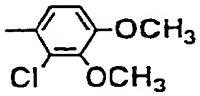
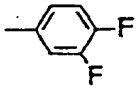
Compound	$-R^1$	$-R^2$	$-Z$	$-R^3$
33	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
34	"	"	"	$-CH_3$
35	"	"		$-H$
36	"	"	"	$-CH_3$
37	"	"		$-H$
38	"	"	"	$-CH_3$
39	"	"		$-H$
40	"	"	"	$-CH_3$
41	"	"		$-H$
42	"	"	"	$-CH_3$
43	"	"		$-H$
44	"	"	"	$-CH_3$
45	"	"		$-H$
46	"	"	"	$-CH_3$
47	"	"		$-H$
48	"	"	"	$-CH_3$
49	"	"		$-H$
50	"	"	"	$-CH_3$
51	$-CH_3$	$-CH_3$	"	$-H$
52	"	"	"	$-CH_3$
53	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
54	"	"	"	$-CH_3$

Table 1-4

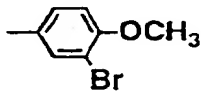
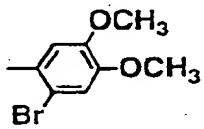
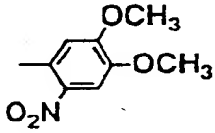
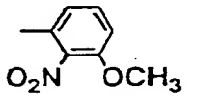
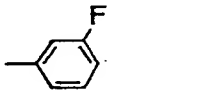
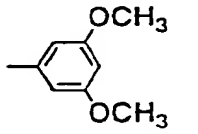
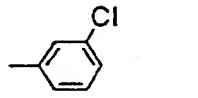
Compound	$-R^1$	$-R^2$	$-Z$	$-R^3$
55	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
56	"	"	"	$-CH_3$
57	$-CH_3$	$-CH_3$	"	$-H$
58	"	"	"	$-CH_3$
59	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
60	"	"	"	$-CH_3$
61	"	"		$-H$
62	"	"	"	$-CH_3$
63	"	"		$-H$
64	"	"	"	$-CH_3$
65	"	"		$-H$
66	"	"	"	$-CH_3$
67	"	"		$-H$
68	"	"	"	$-CH_3$
69	"	"		$-H$
70	"	"	"	$-CH_3$

Table 1-5

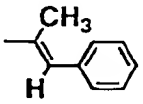
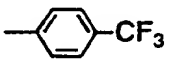
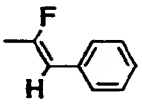
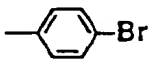
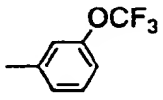
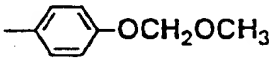
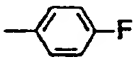
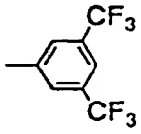
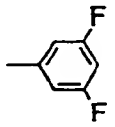
Compound	$-R^1$	$-R^2$	$-Z$	$-R^3$
71	$-CH_2CH_3$	$-CH_2CH_3$	R^4 = 	$-H$
72	"	"	"	$-CH_3$
73	"	"		$-H$
74	"	"	"	$-CH_3$
75	"	"	R^4 = 	$-H$
76	"	"	"	$-CH_3$
77	"	"		$-H$
78	"	"	"	$-CH_3$
79	"	"		$-H$
80	"	"	"	$-CH_3$
81	"	"		$-H$
82	"	"	"	$-CH_3$
83	"	"		$-H$
84	"	"	"	$-CH_3$
85	"	"		$-H$
86	"	"	"	$-CH_3$
87	"	"		$-H$
88	"	"	"	$-CH_3$

Table 1-6

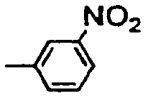
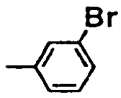
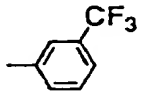
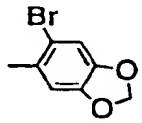
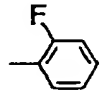
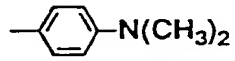
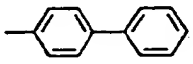
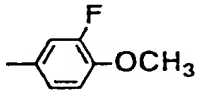
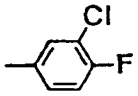
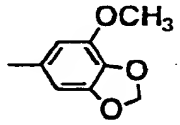
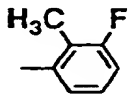
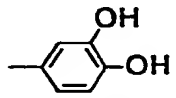
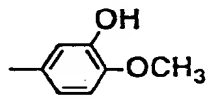
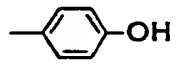
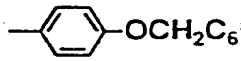
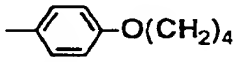
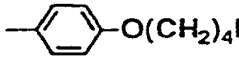
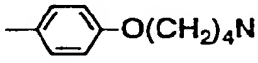
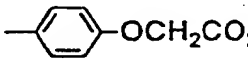
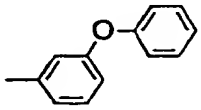
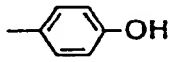
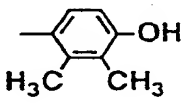
Compound	$-R^1$	$-R^2$	$-Z$	$-R^3$
89	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
90	"	"	"	$-CH_3$
91	"	"		$-H$
92	"	"	"	$-CH_3$
93	"	"		$-H$
94	"	"	"	$-CH_3$
95	"	"		$-H$
96	"	"	"	$-CH_3$
97	"	"		$-H$
98	"	"	"	$-CH_3$
99	"	"		$-H$
100	"	"		"
101	"	"	"	$-CH_3$
102	"	"		$-H$
103	"	"	"	$-CH_3$
104	"	"		$-H$
105	"	"	"	$-CH_3$

Table 1-7

Compound	$-R^1$	$-R^2$	$-Z$	$-R^3$
106	$-CH_2CH_3$	$-CH_2CH_3$		$-H$
107	"	"	"	$-CH_3$
108	"	"		$-H$
109	"	"	"	$-CH_3$
110	"	"		"
111	"	"		"
112	"	"		"
113	"	"		"
114	"	"		"
115	"	"		"
116	"	"		"
117	"	"		"
118	"	"		"
119	"	"		$-H$
120	"	"	"	$-CH_3$
121	"	"		$-H$
122	"	"		$-CH_3$

The pharmacological activities of Compounds (I) are shown below by experimental examples.

Experimental Example 1 Acute Toxicity Test

Test compounds were orally administered to groups of dd-strain male mice weighing 20 ± 1 g, each group consisting of three mice. Seven days after the administration, minimum lethal dose (MLD) of each compound was determined by observing the mortality.

The results ar shown in Table 2.

Table 2-1

Compound	MLD(mg/kg)	Compound	MLD(mg/kg)
1	> 300	31	> 100
2	> 300	32	> 100
3	> 300	33	> 300
4	> 300	34	> 300
5	> 100	35	> 100
6	> 300	36	> 300
7	> 300	37	> 100
8	> 300	38	> 300
9	> 300	39	> 100
10	> 300	40	> 300
11	> 300	41	> 100
12	> 300	42	> 100
13	> 300	43	> 100
14	> 300	44	> 100
15	> 300	45	> 100
16	> 300	46	> 100
17	> 100	47	> 100
18	> 300	48	> 100
19	> 300	49	> 100
20	> 300	50	> 300
21	> 100	51	> 100
22	> 100	52	> 300
23	> 300	53	> 300
24	> 300	54	> 300
25	> 100	55	> 100
26	> 300	56	> 100
27	> 100	57	> 100
28	> 300	58	> 300
29	> 100	59	> 100
30	> 100	60	> 100

Table 2-2

Compound	MLD(mg/kg)	Compound	MLD(mg/kg)
61	> 100	92	> 100
62	> 300	93	> 100
63	> 300	94	> 100
64	> 100	95	> 100
65	> 100	96	> 100
66	> 300	97	> 100
67	> 100	98	> 100
68	> 300	99	> 100
69	> 100	100	> 100
70	> 300	101	> 100
71	> 100	102	> 100
72	> 300	103	> 100
73	> 100	104	> 100
74	> 300	105	> 100
75	> 100	106	> 100
76	> 100	107	> 100
77	> 100	108	> 100
78	> 100	109	> 100
79	> 100	110	> 100
80	> 100	111	> 100
81	> 100	112	> 100
82	> 100	113	> 100
83	> 100	114	> 100
84	> 100	115	> 100
85	> 100	116	> 100
86	> 100	117	> 100
87	> 100	118	> 100
88	> 100	119	> 100
89	> 100	120	> 100
90	> 100	121	> 100
91	> 100	122	> 100

As shown in Table 2, the MLD values of all the compounds are greater than 100 mg/kg or 300 mg/kg, indicating that the toxicity of the compounds is weak. Therefore, these compounds can be safely used in a wide range of doses.

Experimental Example 2 Adenosine Receptor Antagonistic Activity

1) Adenosine A_1 Receptor Binding Test

The test was conducted according to the method of Bruns et al. [Proc. Natl. Acad. Sci., 77, 5547 (1980)] with slight modification.

Cerebrum of a guinea pig was suspended in ice-cooled 50 mM Tris hydroxymethyl aminomethane hydrochloride (Tris HCl) buffer (pH 7.7) by using Polytron homogenizer (manufactured by Kinematicas Co.). The suspension was centrifuged (50,000 x g, 10 minutes), and the precipitate was suspended again in the same amount of 50 mM Tris HCl buffer. The suspension was centrifuged under the same conditions, and the final precipitate was suspended once again in 50 mM Tris HCl buffer to give a tissue concentration of 100 mg (wet weight)/ml. The tissue suspension was incubated at 37°C for 30 minutes in the presence of 0.02 unit/mg tissue of adenosine deaminase (manufactured by Sigma Co.). The tissue suspension was then centrifuged (50,000 x g, 10 minutes), and 50 mM Tris HCl buffer was added to the precipitate to adjust the concentration of tissue to 10 mg (wet weight)/ml.

To 1 ml of the tissue suspension thus prepared were added 50 µl of cyclohexyladenosine labeled with tritium (^{3}H-CHA: 27 Ci/mmol, manufactured by New England Nuclear Co.) (final concentration: 1.1 nM) and 50 µl of a test compound. The mixture solution was allowed to stand at 25°C for 90 minutes and then rapidly filtered by suction through a glass fiber filter (GF/C manufactured by Whatman Co.). The filter was immediately washed three times with 5 ml each of ice-cooled 50 mM Tris HCl buffer, and transferred to a vial, and a scintillator (EX-H by Wako Pure Chemical Industries, Ltd.) was added thereto. The radioactivity on the filter was determined with a liquid scintillation counter (manufactured by Packard Instrument Co.).

The inhibition rate of the test compound against the binding of A_1 receptor (^{3}H-CHA binding) was calculated by the following equation:

$$\text{Inhibition Rate (\%)} = \left(1 - \frac{[B] - [N]}{[T] - [N]}\right) \times 100$$

[Notes]

1. "B" means the amount of radioactivity of ^{3}H-CHA bound in the presence of a test compound at a concentration shown in Table 3.
2. "T" means the amount of radioactivity of ^{3}H-CHA bound in the absence of a test compound.
3. "N" means the amount of radioactivity of ^{3}H-CHA bound in the presence of 10 µM N^6-(L-2-phenylisopropyl)adenosine (manufactured by Sigma Co.).

The results are shown in Table 3. The inhibition constant (Ki value) shown in the table was calculated by the Cheng-Prusoff's equation.

Table 3

Compound	A_1 Receptor		
	Inhibition (%)		K_i(nM)
	10^{-5}M	10^{-4}M	
1	84	86	
2	67	62	
4	55	70	
7	34	49	> 10,000
8	89	94	
9	14	26	>100,000
10	57	56	
13	59	71	
14	84	86	
15	25	35	>100,000
16	53	72	
17	23	31	>100,000
18	56	66	
19	10	31	>100,000
20	11	1	>100,000
21	36	40	>100,000
22	1	1	>100,000
23	32	38	>100,000
24	-4	-25	>100,000

2) Adenosine A_2 Receptor Binding test

The test was conducted according to the method of Bruns et al. [Mol. Pharmacol., 29, 331 (1986)] with slight modification.

The similar procedure as in the above-described adenosine A_1 receptor binding test was repeated using rat corpus striatum to obtain the final precipitate of the tissue thereof. The precipitate was suspended in 50 mM Tris HCl buffer containing 10 mM magnesium chloride and 0.02 unit/mg tissue of adenosine deaminase (manufactured by Sigma Co.) to give a tissue concentration of 5 mg (wet weight)/ml.

To 1 ml of the tissue suspension thus prepared were added 50 µl of a mixture of N-ethylcarboxamidoadenosine labeled with tritium (^{3}H-NECA: 26 Ci/mmol, manufactured by Amersham Co.) (final concentration: 3.8 nM) and cyclopentyladenosine (CPA, manufactured by Sigma Co.) (final concentration: 50 nM), and 50 µl of a test compound. The mixture solution was allowed to stand at 25°C for 120 minutes and then treated in the same manner as in the adenosine A_1 receptor binding test to determine the radioactivity bound to the A_2 receptors.

The inhibition rate of the test compound against the binding of A_2 receptor (^{3}H-NECA binding) was calculated by the following equation:

$$\text{Inhibition Rate (\%)} = \left(1 - \frac{[B] - [N]}{[T] - [N]}\right) \times 100$$

[Notes]

1. "B" means the amount of radioactivity of ^{3}H-NECA bound in the presence of a test compound at a concentration shown in Table 4.
2. "T" means the amount of radioactivity of ^{3}H-NECA bound in the absence of a test compound.
3. "N" means the amount of radioactivity of ^{3}H-NECA bound in the presence of 100 μM CPA.

The similar procedure as above was repeated to determine the radioactivity bound to the A_2 receptors using 50 μl of CGS 21680 labeled with tritium [^{3}H-2-[p-(2-carboxyethyl)-phenethylamino]-5'-(N-ethylcarboxamide)adenosine: 40 Ci/mmol, manufactured by New England Nuclear Co. (J. Pharmacol. Exp. Ther., 251, 888 (1989)] (final concentration: 4.0 nM) in place of 50 μl of the mixture of N-ethylcarboxamidoadenosine labeled with tritium (^{3}H-NECA: 26 Ci/mmol, manufactured by Amersham Co.) (final concentration: 3.8 nM) and cyclopentyladenosine (CPA, manufactured by Sigma Co.) (final concentration: 50 nM).

The inhibition rate of the test compound against the binding of A_2 receptors (^{3}H-CGS 21680 binding) was calculated by the following equation:

$$\text{Inhibition Rate (\%)} = \left(1 - \frac{[B] - [N]}{[T] - [N]}\right) \times 100$$

[Notes]

1. "B" means the amount of radioactivity of ^{3}H-CGS 21680 bound in the presence of a test compound at a concentration shown in Table 4.
2. "T" means the amount of radioactivity of ^{3}H-CGS 21680 bound in the absence of a test compound.
3. "N" means the amount of radioactivity of ^{3}H-CGS 21680 bound in the presence of 100 μM CPA.

The results are shown in Table 4. The Ki value (^{3}H-NECA binding) shown in the table was calculated by the following equation:

$$Ki = \frac{IC_{50}}{1 + \frac{L}{Kd} + \frac{C}{Kc}}$$

[Notes]

IC_{50}:	Concentration at which the inhibition rate is 50%
L:	Concentration of ^{3}H-NECA
Kd:	Dissociation constant of ^{3}H-NECA
C:	Concentration of CPA
Kc:	Inhibition constant of CPA

Table 4-1

Compd.	A_2 Receptor				K_i (nM)	Ratio (A_1/A_2)
	Inhibition (%)					
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M		
1	53	86	98	100	23	
2	67	79	94	92	12	
4	57	84	88	90	33	
7	65	88	75	83	15	> 670
8	80	99	95	74	3.9	
9	79	84	73	86	3.1	> 32,000
10	91	94	90	93	2.0	
13	77	84	88	95	9.5	
14	85	91	96	98	1.6	
15	53	64	70	70	15	
16	80	96	88	93	6.1	
17	70	69	80	80	6.3	> 16,000
18	84	90	104	98	1.5	
19	65	87	92	91	310	> 320
20	51	83	90	88	50	> 2,000
21	56	68	83	79	22	
22	78	85	78	81	3.0	> 33,000
23	38	60	90	81		
24	62	57	75	85	26	> 3,800

Table 4-2

Compd.	A_2 Receptor Inhibition (%)			
	10^{-7}M	10^{-6}M	10^{-5}M	10^{-4}M
25			76	70
26	27	59	75	79
27			89	90
28	46	80	86	99
31	74	82	89	79
32	83	84	82	98
33			93	92
34	86	93	90	94
49	73	76	108	112
50	88	95	88	93
51			88	91
52	78	88	81	83
54	63	94	95	96
55	56	65	77	81
56	74	92	97	99
58			84	78
60			75	84
63			74	79

Table 4-3

Compd.	A_2 Receptor Inhibition (%)		Compd.	A_2 Receptor Inhibition (%)	
	10^{-7}M	10^{-6}M		10^{-7}M	10^{-6}M
35	54	71	86	29*	73*
36	71	101	87	59*	66*
37	56	60	89	59*	78*
38	71	94	90	85*	94*
39	80*	88*	91	9*	51*
40	88*	98*	92	93*	103*
41	27*	52*	93	53*	85*
42	46*	87*	94	71*	98*
43	68*	70*	95	75*	89*
44	64*	103*	96	84*	101*
47	67*	92*	97	66*	87*
48	83*	99*	98	92*	95*
64	89*	94*	99	25	64
65	64	64	101	36*	76*
66	78	93	102	70*	94*
67	73	73	103	75*	102*
68	81	88	105	76*	96*
70	76	84	106	83*	94*
74	59*	87*	107	93*	84*
76	30	69	108	87*	94*
77	54*	54*	109	97*	96*
78	68*	89*	110	61*	96*
79	53*	79*	112	79*	95*
80	72*	86*	113	34*	68*
81	78*	95*	114	23*	87*
82	86*	98*	115	34*	79*
83	75*	70*	120	89*	75*
84	82*	100*			

*; [^{3}H]CGS 21680 was used.

As shown in Tables 3 and 4, Compounds (I) and pharmaceutically acceptable salts thereof exhibit an extremely potent affinity especially for adenosine A_2 receptors.

Experimental Example 3 Effect on Locomotor Activity in Parkinson's Disease Model in Mice

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is known to cause an acute Parkinson's syndrome (parkinsonism) when administered to humans. The syndrome resembles spontaneous parkinsonism in terms of cardinal symptoms (muscular rigidity, bradycinesia, and resting tremor) and pathological phenomena (ex-

tensive degeneration of the nigrostriatal dopamine system) [Science, 219, 979 (1983)]. MPTP-treated mice also exhibit the syndrome similar to parkinsonism [Science, 224, 1451 (1984)].

Especially, MPTP-treated C57BL/6 mice have been reported to serve as a suitable model for Parkinson's disease. In this strain of mice, striatal dopamine is remarkably decreased and locomotor activity is profoundly depressed [Brain Res., 528, 181 (1990)].

The experiment was performed by using several groups of 7-weeks-old male C57BL/6 mice (weighing 20 to 24 g, Japan SLC), each group consisting of 8 mice. MPTP (Aldrich Chemical Co., Inc.) dissolved in a physiological saline solution (Otsuka Pharmaceutical Co., Ltd.) was intraperitoneally administered to each mouse once a day for five consecutive days at a dose of 30 mg/kg. A test compound was suspended in injectable distilled water (Otsuka Phamaceutical Co., Ltd.) containing Tween 80 [polyoxyethylene (20) sorbitan monooleate]. L-DOPA (Kyowa Hakko Kogyo Co., Ltd.) was suspended in 0.3% CMC (sodium carboxylmethylcellulose) and bromocriptine was suspended in injectable distilled water. Thirty minutes after the final MPTP administration, the test compound suspensions and the control suspension [injectable distilled water (Otsuka Pharmaceutical Co., Ltd.) containing Tween 80] containing no test compound were orally administered to separate groups of the mice (0.1 ml per 10 g of body weight). The amount of active movements (horizontal activity) of each mouse was measured by using Automex-II (Columbus Instruments International Corp.) for the period of 30 minutes starting 30 minutes after the administration of the test compound. Bromocriptine was administerd 3 hours proir to the final MPTP treatment, and the amount of active movements was measured for the period of 30 minutes from 1 hour after the MPTP treatment. The effect of the compounds was evaluated by comparing the average counts of the active movements of the test compound-administered groups with those of the control groups. Statistical comparison of the values was carried out by Student's t-test.

The results are shown in Table 5.

Table 5-1

Group	Administration		Dose of Test Compound (mg/kg)	Amount of Active Movements (average count ± S.E.M)
Normal Control	MPTP	(-)		
	Test Compound	(-)	-	2210 ±101.1
MPTP	MPTP	(+)		
	Test Compound	(-)	-	45 ± 10.7 ##
Compound 2	MPTP	(+)		
	Compound 2	(+)	10	637 ±160.0 *
Compound 8	MPTP	(+)		
	Compound 8	(+)	10	924 ±219.5 **

##: $p<0.01$ (comparison with normal control group)
*: $p<0.05$; **: $p<0.01$ (comparison with MPTP-treated group)

Table 5-2

Group	Administration		Dose of Test Compound (mg/kg)	Amount of Active Movements (average count ± S.E.M)
Normal Control	MPTP	(-)		
	Test Compound	(-)	-	2205 ±232.3
MPTP	MPTP	(+)		
	Test Compound	(-)	-	60 ± 20.8 ##
Compound 2	MPTP	(+)		
	Compound 2	(+)	2.5	1265 ±316.9 **
Compound 8	MPTP	(+)		
	Compound 8	(+)	2.5	800 ±156.8 **

##: p<0.01 (comparison with normal control group)
**: p<0.01 (comparison with MPTP-treated group)

Table 5-3

Group	Administration		Dose of Test Compound (mg/kg)	Amount of Active Movements (average count ± S.E.M)
Normal Control	MPTP	(-)		
	Test Compound	(-)	-	2078 ±180.2
MPTP	MPTP	(+)		
	Test Compound	(-)	-	132 ± 65.3 ##
Compound 2	MPTP	(+)		
	Compound 2	(+)	0.63	610 ±147.9 *

##: p<0.01 (comparison with normal control group)
*: p<0.05 (comparison with MPTP-treated group)

Table 5-4

Group	Administration		Dose of Test Compound (mg/kg)	Amount of Active Movements (average count ± S.E.M)
Normal Control	MPTP	(-)		
	Test Compound	(-)	-	2326 ±147.1
MPTP	MPTP	(+)		
	Test Compound	(-)	-	71 ± 37.2 ##
Compound 10	MPTP	(+)		
	Compound 10	(+)	10	754 ±174.2 **
Compound 14	MPTP	(+)		
	Compound 14	(+)	10	817 ±163.1 **

##: p<0.01 (comparison with normal control group)
**: p<0.01 (comparison with MPTP-treated group)

Table 5-5

Group	Administration		Dose of Test Compound (mg/kg)	Amount of Active Movements (average count ± S.E.M)
Normal Control	MPTP	(-)		
	Test Compound	(-)	-	2574 ±165.9
MPTP	MPTP	(+)		
	Test Compound	(-)	-	21 ± 5.1 ##
Compound 34	MPTP	(+)		
	Compound 34	(+)	10	157 ± 25.0 **

##: p<0.01 (comparison with normal control group)
**: p<0.01 (comparison with MPTP-treated group)

Table 5-6

Group	Administration		Dose of Test Compound (mg/kg)	Amount of Active Movements (average count ± S.E.M)
Normal Control	MPTP Test Compound	(−) (−)	−	2349 ±121.7
MPTP	MPTP Test Compound	(+) (−)	−	44 ± 14.4 ##
Compound 20	MPTP Compound 20	(+) (+)	2.5	937 ±189.5 **
Compound 107	MPTP Compound 107	(+) (+)	2.5	604 ±192.6 *

##: $p<0.01$ (comparison with normal control group)
*: $p<0.05$; **: $p<0.01$ (comparison with MPTP-treated group)

Table 5-7

Group	Administration		Dose of Test Compound (mg/kg)	Amount of Active Movements (average count ± S.E.M)
Normal Control	MPTP Test Compound	(−) (−)	−	1875 ± 77.7
MPTP	MPTP Test Compound	(+) (−)	−	207 ± 85.5 ##
L-DOPA	MPTP L-DOPA	(+) (+)	300	561 ±271.01[1)]

##: $p<0.01$ (comparison with normal control group)
1): no significant difference as compared with MPTP-treated group)

Table 5-8

Group	Administration		Dose of Test Compound (mg/kg)	Amount of Active Movements (average count ± S.E.M)
Normal Control	MPTP Test Compound	(-) (-)	-	1984 ±122.3
MPTP	MPTP Test Compound	(+) (-)	-	41 ± 14.3 ##
Bromo-criptine	MPTP Bromocriptine	(+) (+)	40	1739 ±494.9 **

##: p<0.01 (comparison with normal control group)
**: p<0.01 (comparison with MPTP-treated group)

Table 5-9

Group	Administration		Dose of Test Compound (mg/kg)	Amount of Active Movements (average count ± S.E.M)
Normal Control	MPTP Test Compound	(-) (-)	-	2574 ±165.9
MPTP	MPTP Test Compound	(+) (-)	-	21 ± 5.1 ##
Bromo-criptine	MPTP Bromocriptine	(+) (+)	10	66 ± 35.4 1)

##: p<0.01 (comparison with normal control group)
1): no significant difference as compared with MPTP-treated group)

As shown in Table 5, L-DOPA (metabolic precursor of dopamine) and bromocriptine (dopamine receptor agonist), which are conventionally used drugs for Prakinson's disease, exhibited only a weak inhibitory activity against the depression of locomotor activity caused by MPTP by oral administration at a dose of 300 and 40 mg/kg, respectively. On the other hand, Compounds (I) showed a potent inhibitory activity at a dose of 10 mg/kg or less than 10 mg/kg.

Experimental Example 4 Effect on Haloperidol-Induced Catalepsy

Parkinson's disease is a clinical syndrome caused by degeneration of nigrostriatal dopaminergic neurons. Systemic administration of haloperidol (dopamine D_1/D_2 antagonist) induces catalepsy resulting from the blockade of postsynaptic dopamine D_2 receptors. It is generally accepted that this haloperidol-induced catalepsy is a classical model of parkinsonism in humans [Eur. J. Pharmacol., 182, 327 (1990)].

The experiment was performed by using several groups of 5-weeks-old male ddY mice (weighing 22 to 24 g, Japan SLC), each group consisting of 5 mice. Haloperidol (Janssen Pharmaceutica) suspended in 0.3% CMC was intraperitoneally administered to each mous at a dose of 1.0 mg/kg. Test compounds were suspended in 0.3% CMC or in injectable distilled water (Otsuka Pharmaceutical Co., Ltd.) containing Tween 80. L-DOPA (Kyowa Hakko Kogyo Co., Ltd.) and benserazide hydrochloride (Kyowa Hakko Kogyo Co., Ltd.) were

suspended in 0.3% CMC. One hour after the haloperidol administration, the test compound suspensions and the control suspension [injectable distilled water (Otsuka Pharmaceutical Co., Ltd.) containing Tween 80] containing no test compound were orally administered to separate groups of the mice (0.1 ml per 10 g of body weight). One hour after the administration of the test compound, the forelimbs of each mouse and subsequently the hindlimbs of the same mouse were placed on a 4.5 cm-high, 1.0 cm-wide bar and catalepsy was estimated. All of the test compounds were orally administered at a dose of 10 mg/kg, and L-DOPA (100 mg/kg) and benserazide (25 mg/kg) were intraperitoneally administered together as a control experiment. The catalepsy score and the standard of judgment are shown below.

score	duration of the cataleptic posture	
0:	forelimbs	less than 5 seconds
	hindlimbs	less than 5 seconds
1:	forelimbs	from 5 (inclusive) to 10 (exclusive) seconds
	hindlimbs	less than 5 seconds
2:	forelimbs	10 seconds or more
	hindlimbs	less than 5 seconds
3:	forelimbs	from 5 (inclusive) to 10 (exclusive) seconds
	hindlimbs	from 5 (inclusive) to 10 (exclusive) seconds;
	or forelimbs	less than 5 seconds
	hindlimbs	5 seconds or more
4:	forelimbs	10 seconds or more
	hindlimbs	from 5 (inclusive) to 10 (exclusive) seconds;
	or forelimbs	from 5 (inclusive) to 10 (exclusive) seconds
	hindlimbs	10 seconds or more
5:	forelimbs	10 seconds or more
	hindlimbs	10 seconds or more

The effect of the compounds was evaluated by the total of the catalepsy scores of five mice in each group (25 points at the full). The groups wherein the total score was not more than 20 points were estimated to be effective. The number of the animals showing remission against catalepsy is the number of the mice for which the catalepsy score was not more than 4 points. The remission rate shows the rate of decrease in total score based on that of the control group.

The ED_{50} (50% effective dose) values were determined using ten mice at each dose. A test compound was judged to be effective at the dose where the catalepsy score was 3 or less than 3. The ED_{50} values were calculated by Probit analysis.

The results are shown in Table 6.

Table 6-1

Compound	Total Score	Number of the Animals Showing Remission	Remission Rate (%)	ED_{50} (mg/kg)
0.3% Tween 80 (Control)	25	0	0	
L-DOPA + benserazide	18	4	28	107.5
2	2	5	80	0.03
6	6	5	76	1.7
8	2	5	92	0.23
10	8	5	68	0.24
12	12	5	52	2.7
14	1	5	92	0.6
16	4	5	84	0.76
18	4	5	84	1.9
20	7	5	72	0.35
21	19	4	24	
22	20	3	20	
31	16	4	36	
32	17	4	32	
34	8	5	68	2.6
36	6	5	76	1.5
38	8	4	68	2.5
40	3	5	88	
44	17	3	32	
50	19	4	24	3.8
52	10	5	60	1.7

Table 6-2

Compound	Total Score	Number of the Animals Showing Remission	Remission Rate (%)	ED_{50} (mg/kg)
0.3% Tween 80 (Control)	25	0	0	
L-DOPA + benserazide	18	4	28	107.5
54	18	5	28	
56	14	5	44	
63	17	3	32	
64	16	4	36	
67	9	5	64	
68	5	5	80	
70	14	4	44	
76	15	4	40	
78	18	3	28	
82	9	5	64	
84	17	4	32	
86	16	3	36	
90	14	4	44	
92	12	4	52	
103	16	3	36	
107	3	5	92	0.01
109	4	5	84	
110	20	3	20	
112	4	5	84	
113	19	3	24	

Experimental Example 5 Augmentation of the Contralateral Rotation in Rats with a 6-Hydroxydopamine-Induced Unilateral Lesion of the Nigrostriatal Dopamine Pathway

When a unilateral lesion of the nigrostriatal pathway is induced by 6-hydroxydopamine in rodents, the sensitivity of dopamine receptors in the denervated striatum is enhanced. Administration of a dopamine agonist to the rodents in such a condition induces a rotational behavior to the side contralateral to the lesioned sid [Acta Physiol. Scand., 367, 69 (1971)]. This model has b en us d for a long time as a model for th study of Parkinson's dis ase and in the screening of drugs for this disease [Neurol. Neurobiol., 33, 1 (1987)].

Mal Sprague-Dawley rats (weighing 200 to 240 g, Japan SLC) were pretreated with desipramine hydrochloride (25 mg/kg, i.p., Sigma Co.) 30 minut s before surgery to protect noradrenergic n urons. Then, th animals were anesth tized with sodium pentobarbital (30 mg/kg, i.p., Dainippon Pharm. Co., Ltd.) and the nigrostriatal pathway was lesioned by injection of 6-hydroxydopamine hydrobromide (8 µg, Sigma Co.) into the

left medial forebrain bundle. 6-Hydroxydopamine hydrobromide was dissolved in physiological saline containing 0.05% L-ascorbic acid (Wako Pure Chem. Industries, Ltd.) to make 2 µl of solution and injected over 3 minutes.

More than 10 days after surgery, each rat was placed in a plastic bowl (30 cm in diameter). Apomorphine (0.1 mg/kg, Sandoz, AG) was injected subcutaneously and the rats which showed a rotational behavior to the side contralateral to the lesioned side at a frequency of more than 600 counts/60 minutes after apomorphine administration were used for screening. The number of rotations was counted with an automated rotometer, in which each 180° turn was counted as a rotation.

Test compounds were suspended in 0.3% sodium carboxymethylcellulose and administered orally at a dose of 1 mg/kg 30 minutes before the injection of apomorphine (0.1 mg/kg, s.c.). The counts of rotations were summed up every 5 minutes for 150 minutes after apomorphine administration. The total rotation counts induced by apomorphine (0.1 mg/kg, s.c.) with and without a test compound were statistically compared, using the same animals. Rats were allowed to rest more than 5 days between each experiment. Statistical comparison of the values was carried out by Sign-Wilcoxon test.

The results are shown in Table 7.

Table 7

Compd.	total amount of rotations (average count ± S.E.M.)	
	apomorphine	test compound + apomorphine
2	1102 ± 94	1584 ± 196*
8	1003 ± 84	1406 ± 155*
10	1097 ± 147	1637 ± 127*
14	1006 ± 81	1378 ± 216*
107	1041 ± 51	1490 ± 146*

* : $p<0.05$

Compounds (I) and pharmaceutically acceptable salts thereof can be administered as they are, or in the form of various pharmaceutical compositions. The pharmaceutical compositions in accordance with the present invention can be prepared by uniformly mixing an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient, with a pharmaceutically acceptable carrier. It is desired that such pharmaceutical compositions are prepared in a unit dose form suitable for oral administration or administration through injection.

For preparing a pharmaceutical composition for oral administration, any useful pharmaceutically acceptable carrier can be used. For example, liquid preparations for oral administration such as suspension and syrup can be prepared using water, sugars such as sucrose, sorbitol and fructose, glycols such as polyethylene glycol and propylene glycol, oils such as sesame oil, olive oil and soybean oil, preservatives such as p-hydroxybenzoates, flavors such as strawberry flavor and peppermint, and the like. Powders, pills, capsules and tablets can be prepared using excipients such as lactose, glucose, sucrose and mannitol, disintegrating agents such as starch and sodium alginate, lubricants such as magnesium stearate and talc, binders such as polyvinyl alcohol, hydroxypropyl cellulose and gelatin, surfactants such as fatty acid esters, plasticizers such as glycerin, and the like. Tablets and capsules are most useful oral unit dose forms because of the readiness of administration. For preparing tablets and capsules, solid pharmaceutical carriers are used.

Solutions of injectable preparations can be prepared using a carrier such as distilled water, a salt solution, a glucose solution or a mixture of a salt solution and a glucose solution. The preparations can be prepared in the form of solution, suspension or dispersion according to a conventional method by using a suitable auxiliary.

Compounds (I) and pharmaceutically acceptable salts thereof can be administered orally in the said dosage forms or parenterally as injections. The effective dose and the administration schedule vary depending upon mode of administration, age, body weight and conditions of a patient, etc. However, generally, Compound (I) or a pharmaceutically acceptable salt thereof is administered in a daily dose of 0.01 to 25 mg/kg in 3 to 4 parts.

In addition, Compounds (I) may also be administered by inhalation in the form of aerosol, fine powder, or

spray solution. In the case of aerosol administration, the compound of the present invention is dissolved in an appropriate pharmaceutically acceptable solvent such as ethyl alcohol and a combination of miscible solvents, and the resulting solution is mixed with a pharmaceutically acceptable propellant.

Certain embodiments of the invention are illustrated in the following examples and reference examples.

Example 1

(E)-8-(3,4-Dimethoxystyryl)-1,3-diethylxanthine (Compound 1)

3,4-Dimethoxycinnamic acid (1.39 g, 6.67 mmol) and 3-(3-diethylaminopropyl)-1-ethylcarbodiimide hydrochloride (1.74 g, 9.09 mmol) were added to a mixture of dioxane (40 ml) and water (20 ml) containing 5,6-diamino-1,3-diethyluracil [J. Am. Chem. Soc., 75, 114 (1953)] (1.20 g, 6.06 mmol). The resultant solution was stirred at room temperature for 2 hours at pH 5.5. After neutralization, the reaction solution was extracted three times with 50 ml of chloroform. The combined extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure.

To the residue were added 10 ml of dioxane and 15 ml of an aqueous 1N sodium hydroxide solution, followed by heating under reflux for 20 minutes. After cooling, the solution was neutralized and 20 ml of chloroform was added thereto. The organic layer was separated and the aqueous layer was extracted twice with 20 ml of chloroform. The combined extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 2% methanol/chloroform), followed by recrystallization from toluene to give 1.06 g (yield 47%) of Compound 1 as pale yellow needles.

Melting Point: 268.8-269.1°C

Elemental Analysis: $C_{19}H_{22}N_4O_4$

Calcd. (%): C, 61.61; H, 5.98; N, 15.12

Found (%): C, 61.99; H, 6.00; N, 14.91

IR (KBr) ν_{max} (cm^{-1}): 1694, 1641, 1514, 1492

NMR (270MHz; DMSO-d_6) δ (ppm): 13.35(1H, brs), 7.59 (1H, d, J=16.2Hz), 7.27(1H, d, J=1.4Hz), 7.14(1H, dd, J=1.4, 8.2Hz), 6.99(1H, d, J=8.2Hz), 6.96(1H, d, J=16.2Hz), 4.06(2H, q, J=7.0Hz), 3.91(2H, q, J=7.0Hz), 3.83(3H, s), 3.79(3H, s), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=7.0Hz)

Example 2

(E)-8-(3,4-Dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 2)

Compound 1 (1.20 g, 3.24 mmol) obtained in Example 1 was dissolved in 25 ml of dimethylformamide. To the solution were added 1.12 g (8.10 mmol) of potassium carbonate and subsequently 0.40 ml (6.49 mmol) of methyl iodide, and the resultant mixture was stirred at 50°C for 30 minutes. After cooling, insoluble matters were filtered off, and 100 ml of water was added to the filtrate. The mixture was extracted three times with 50 ml of chloroform. The extract was washed twice with water and once with a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The obtained crude crystals were purified by silica gel column chromatography (eluent: 40% ethyl acetate/hexane), followed by recrystallization from isopropanol to give 840 mg (yield 68%) of Compound 2 as pale yellow needles.

Melting Point: 190.4-191.3°C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.48;	H, 6.29;	N, 14.57
Found (%):	C, 62.52;	H, 6.53;	N, 14.56

IR (KBr) ν_{max} (cm^{-1}): 1697, 1655, 1518

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.5Hz), 7.18(1H, dd, J=1.9, 8.3Hz), 7.08(1H, d, J=1.9Hz), 6.89(1H, d, J=8.3Hz), 6.77(1H, d, J=15.5Hz), 4.21 (2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.06(3H, s), 3.96(3H, s), 3.93(3H, s), 1.39(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Example 3

(E)-8-(2,3-Dimethoxystyryl)-1,3-diethylxanthine (Compound 3)

Substantially the same procedure as in Example 1 was repeated using 2.0 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.52 g (12.1 mmol) of 2,3-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylsulfoxide/water to give 1.72 g (yield 46%) of Compound 3 as a white powder.

Melting Point: 287.5-289.4°C

Elemental Analysis: $C_{19}H_{22}N_2O_4$			
Calcd. (%):	C, 61.61;	H, 5.98;	N, 15.12
Found (%):	C, 61.56;	H, 6.11;	N, 14.83

IR (KBr) ν_{max} (cm^{-1}): 1697, 1656, 1500

NMR (270MHz; DMSO-d_6) δ (ppm): 13.64(1H, brs), 7.84 (1H, d, J=16.8Hz), 7.29(1H, dd, J=1.7, 7.6Hz), 7.15-7.00(3H, m), 4.07(2H, q, J=7.0Hz), 3.94(2H, q, J=7.0Hz), 3.83(3H, s), 3.79(3H, s), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=7.0Hz)

Example 4

(E)-8-(2,3-Dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 4)

Substantially the same procedure as in Example 2 was repeated using 1.60 g (4.32 mmol) of Compound 3 obtained in Example 3 in place of Compound 1. Then, the resultant crude crystals were recrystallized from cyclohexane/toluene to give 1.21 g (yield 73%) of Compound 4 as a pale yellow powder.

Melting Point: 194.9-195.6°C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.48;	H, 6.29;	N, 14.57
Found (%):	C, 62.67;	H, 6.48;	N, 14.31

IR (KBr) ν_{max} (cm^{-1}): 1694, 1660, 1272

NMR (270MHz; $CDCl_3$) δ (ppm): 8.00(1H, d, J=16.8Hz), 7.19(1H, dd, J=1.3, 7.9Hz), 7.15-7.00(2H, m), 6.93 (1H, dd, J=1.3, 7.9Hz), 4.26(2H, q, J=6.9Hz), 4.09 (2H, q, J=6.9Hz), 4.05(3H, s), 3.91(3H, s), 3.90 (3H, s), 1.39(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Example 5

(E)-8-(2,4-Dimethoxystyryl)-1,3-diethylxanthine (Compound 5)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.89 g (13.9 mmol) of 2,4-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/ethanol to give 0.92 g (yield 20%) of Compound 5 as yellow crystals.

Melting Point: 278.7-279.8°C

Elemental Analysis: $C_{19}H_{22}N_4O_4$			
Calcd. (%):	C, 61.61;	H, 5.98;	N, 15.12
Found (%):	C, 61.65;	H, 5.95;	N, 14.74

IR (KBr) ν_{max} (cm^{-1}): 1698, 1640, 1509, 1292

NMR (270MHz; DMSO-d_6) δ (ppm): 13.43(1H, brs), 7.77 (1H, d, J=16.8Hz), 7.54(1H, d, J=8.4Hz), 6.95(1H, d, J=16.8Hz), 6.63(1H, d, J=2.5Hz), 6.60(1H, dd, J=2.5, 8.4Hz), 4.06(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 3.89(3H, s), 3.82(3H, s), 1.25(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Example 6

(E)-8-(2,4-Dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 6)

Substantially the same procedure as in Example 2 was repeated using 400 mg (1.08 mmol) of Compound 5 obtained in Example 5 in place of Compound 1. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 335 mg (yield 81%) of Compound 6 as yellow needles.

Melting Point: 195.9-196.7°C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.48;	H, 6.29;	N, 14.57
Found (%):	C, 62.29;	H, 6.51;	N, 14.66

IR (KBr) ν_{max} (cm^{-1}): 1693, 1654, 1603, 1294

NMR (270MHz; $CDCl_3$) δ (ppm): 7.93(1H, d, J=15.8Hz), 7.48(1H, d, J=8.3Hz), 6.97(1H, d, J=15.8Hz), 6.53 (1H, dd, J=2.0, 8.3Hz), 6.49(1H, d, J=2.0Hz), 4.22 (2H, q, J=6.9Hz), 4.08(2H, q, J=6.9Hz), 4.02(3H, s), 3.92(3H, s), 3.86(3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Example 7

(E)-1,3-Diethyl-8-(2,3,4-trimethoxystyryl)xanthine (Compound 7)

Substantially the same procedure as in Example 1 was repeated using 2.5 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.3 g (13.9 mmol) of 2,3,4-trimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.85 g (yield 57%) of Compound 7 as white crystals.

Melting Point: 276.3-277.0°C

Elemental Analysis: $C_{20}H_{24}N_4O_5$

Calcd. (%): C, 59.99; H, 6.04; N, 13.99

Found (%): C, 60.26; H, 6.24; N, 14.28

IR (KBr) ν_{max} (cm^{-1}): 1696, 1655, 1500

NMR (270MHz; $CDCl_3$) δ (ppm): 12.39(1H, brs), 7.88(1H, d, J=16.3Hz), 7.30(1H, d, J=8.4Hz), 7.09(1H, d, J=16.3Hz), 6.73(1H, d, J=8.4Hz), 4.26(2H, q, J=6.9Hz), 4.20(2H, q, J=6.9Hz), 3.96(3H, s), 3.92 (3H, s), 3.91(3H, s), 1.41(3H, t, J=6.9Hz), 1.29 (3H, t, J=6.9Hz)

Example 8

(E)-1,3-Diethyl-7-methyl-8-(2,3,4-trimethoxystyryl)xanthine (Compound 8)

Substantially the same procedure as in Example 2 was repeated using 1.5 g (3.75 mmol) of Compound 7 obtained in Example 7 in place of Compound 1. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.32 g (yield 85%) of Compound 8 as colorless needles.

Melting Point: 152.9-154.3°C

Elemental Analysis: $C_{21}H_{26}N_4O_5$			
Calcd. (%):	C, 60.86;	H, 6.32;	N, 13.52
Found (%):	C, 61.04;	H, 6.44;	N, 13.79

IR (KBr) ν_{max} (cm^{-1}): 1695, 1655, 1498, 1289

NMR (270MHz; $CDCl_3$) δ (ppm): 7.88(1H, d, J=15.8Hz), 7.28(1H, d, J=8.9Hz), 7.01(1H, d, J=15.8Hz), 6.72 (1H, d, J=8.9Hz), 4.22(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 3.97(3H, s), 3.91(3H, s), 3.90(3H, s), 1.38(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Example 9

(E)-1,3-Diethyl-8-(4-methoxy-2,3-dimethylstyryl)xanthine (Compound 9)

Substantially the same procedure as in Example 1 was repeated using 2.5 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.9 g (13.9 mmol) of 4-methoxy-2,3-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/water to give 0.80 g (yield 17%) of Compound 9 as white crystals.

Melting Point: >280.0°C

Elemental Analysis: $C_{20}H_{24}N_4O_3$			
Calcd. (%):	C, 65.20;	H, 6.56;	N, 15.21
Found (%):	C, 65.24;	H, 6.61;	N, 15.29

IR (KBr) ν_{max} (cm^{-1}): 1697, 1642, 1496, 1270

NMR (270MHz; DMSO-d_6) δ (ppm): 13.52(1H, brs), 7.93 (1H, d, J=15.8Hz), 7.56(1H, d, J=8.2Hz), 6.89(1H, d, J=8.2Hz), 6.82(1H, d, J=15.8Hz), 4.06(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 3.81(3H, s), 2.33 (3H, s), 2.13(3H, s), 1.26(3H, t, J=6.9Hz), 1.14 (3H, t, J=6.9Hz)

Example 10

(E)-1,3-Diethyl-8-(4-methoxy-2,3-dimethylstyryl)-7-methylxanthine (Compound 10)

Substantially the same procedure as in Example 2 was repeated using 500 mg (1.36 mmol) of Compound 9 obtained in Example 9 in place of Compound 1. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 493 mg (yield 95%) of Compound 10 as pale yellow needles.

Melting Point: 207.7-208.3°C

Elemental Analysis: $C_{21}H_{26}N_4O_3$			
Calcd. (%):	C, 65.95;	H, 6.85;	N, 14.65
Found (%):	C, 66.24;	H, 6.99;	N, 14.69

IR (KBr) ν_{max} (cm^{-1}): 1698, 1651, 1267

NMR (270MHz; $CDCl_3$) δ (ppm): 8.08(1H, d, J=15.2Hz), 7.46(1H, d, J=8.9Hz), 6.77(1H, d, J=8.9Hz), 6.67 (1H, d, J=15.2Hz), 4.22(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.03(3H, s), 3.86(3H, s), 2.40(3H, s), 2.21(3H, s), 1.39(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Example 11

(E)-1,3-Diethyl-8-(4-methoxy-2,5-dimethylstyryl)xanthine (Compound 11)

Substantially the same procedure as in Example 1 was repeated using 2.5 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.9 g (13.9 mmol) of 4-methoxy-2,5-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.43 g (yield 52%) of Compound 11 as white crystals.

Melting Point: >280.0°C

Elemental Analysis: $C_{20}H_{24}N_4O_3$			
Calcd. (%):	C, 65.20;	H, 6.56;	N, 15.21
Found (%):	C, 64.83;	H, 6.56;	N, 15.43

IR (KBr) ν_{max} (cm^{-1}): 1690, 1646, 1510, 1265

NMR (270MHz; DMSO-d_6) δ (ppm): 13.52(1H, brs), 7.82 (1H, d, J=16.3Hz), 7.54(1H, s), 6.86(1H, d, J=16.3Hz), 6.82(1H, s), 4.06(2H, q, J=6.9Hz), 3.94 (2H, q, J=6.9Hz), 3.81(3H, s), 2.41(3H, s), 2.14 (3H, s), 1.25(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Example 12

(E)-1,3-Diethyl-8-(4-methoxy-2,5-dimethylstyryl)-7-methylxanthine (Compound 12)

Substantially the same procedure as in Example 2 was repeated using 1.10 g (2.98 mmol) of Compound 11 obtained in Example 11 in place of Compound 1. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 0.76 g (yield 67%) of Compound 12 as yellow needles.

Melting Point: 235.4-236.1°C

Elemental Analysis: $C_{21}H_{26}N_4O_3$			
Calcd. (%):	C, 65.95;	H, 6.85;	N, 14.65
Found (%):	C, 65.56;	H, 6.93;	N, 14.64

IR (KBr) ν_{max} (cm^{-1}): 1689, 1657, 1510, 1263

NMR (270MHz; $CDCl_3$) δ (ppm): 7.97(1H, d, J=15.5Hz), 7.42(1H, s), 6.71(1H, d, J=15.5Hz), 6.66(1H, s), 4.22(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.05 (3H, s), 3.86(3H, s), 2.48(3H, s), 2.23(3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Example 13

(E)-8-(2,4-Dimethoxy-3-methylstyryl)-1,3-diethylxanthine (Compound 13)

Substantially the same procedure as in Example 1 was repeated using 2.0 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.04 g (9.19 mmol) of 2,4-dimethoxy-3-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.22 g (yield 32%) of Compound 13 as a yellow powder.

Melting Point: >275.0°C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.48;	H, 6.29;	N, 14.57
Found (%):	C, 62.28;	H, 6.42;	N, 14.22

IR (KBr) ν_{max} (cm^{-1}): 1696, 1635, 1592, 1499

NMR (270MHz; DMSO-d_6) δ (ppm): 7.75(1H, d, J=16.5Hz), 7.58(1H, d, J=8.8Hz), 6.99(1H, d, J=16.5Hz), 6.85 (1H, d, J=8.8Hz), 4.04(2H, q, J=6.9Hz), 3.95(2H, q, J=6.9Hz), 3.83(3H, s), 3.70(3H, s), 2.09(3H, s), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Example 14

(E)-8-(2,4-Dimethoxy-3-methylstyryl)-1,3-diethyl-7-methylxanthine (Compound 14)

Substantially the same procedure as in Example 2 was repeated using 700 mg (1.82 mmol) of Compound 13 obtained in Example 13 in place of Compound 1. Then, the resultant crude crystals were recrystallized from cyclohexane/toluene to give 610 mg (yield 84%) of Compound 14 as pale yellow needles.

Melting Point: 196.1-196.8°C

Elemental Analysis: $C_{21}H_{26}N_4O_4$			
Calcd. (%):	C, 63.30;	H, 6.57;	N, 14.06
Found (%):	C, 63.32;	H, 6.74;	N, 14.13

IR (KBr) ν_{max} (cm^{-1}): 1695, 1649, 1498

NMR (270MHz; $CDCl_3$) δ (ppm): 7.81(1H, d, J=15.8Hz), 7.78 (1H, d, J=8.6Hz), 7.23(1H, d, J=15.8Hz), 6.87 (1H, d, J=8.6Hz), 4.07(2H, q, J=6.9Hz), 4.01(3H, s), 3.92(2H, q, J=6.9Hz), 3.85(3H, s), 3.70(3H, s), 2.10(3H, s), 1.27(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Example 15

(E)-1,3-Diethyl-8-(3,4-methylenedioxystyryl)xanthine (Compound 15)

Substantially the same procedure as in Example 1 was repeated using 2.0 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.33 g (12.1 mmol) of 3,4-methylenedioxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/water to give 1.34 g (yield 38%) of Compound 15 as a yellowish green powder.

Melting Point: >275.0°C

Elemental Analysis: $C_{18}H_{18}N_4O_4$

Calcd. (%): C, 61.01; H, 5.11; N, 15.81

Found (%): C, 61.16; H, 5.03; N, 15.80

IR (KBr) ν_{max} (cm^{-1}): 1685, 1638, 1499

NMR (270MHz; DMSO-d_6) δ (ppm): 7.55(1H, d, J=16.3Hz), 7.30(1H, s), 7.08(1H, d, J=8.9Hz), 6.96(1H, d, J=8.9Hz), 6.90(1H, d, J=16.3Hz), 6.07(2H, s), 4.05 (2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 1.25(3H, t, J=6.9Hz), 1.10(3H, t, J=6.9Hz)

Example 16

(E)-1,3-Diethyl-7-methyl-8-(3,4-methylenedioxystyryl)xanthine (Compound 16)

Substantially the same procedure as in Example 2 was repeated using 1.35 g (3.81 mmol) of Compound 15 obtained in Example 15 in place of Compound 1. Then, the resultant crude crystals were recrystallized from cyclohexane/toluene to give 940 mg (yield 67%) of Compound 16 as yellow needles.

Melting Point: 219.4-219.6°C

Elemental Analysis: $C_{19}H_{20}N_4O_4$			
Calcd. (%):	C, 61.94;	H, 5.47;	N, 15.20
Found (%):	C, 62.09;	H, 5.41;	N, 15.16

IR (KBr) ν_{max} (cm^{-1}): 1687, 1657, 1569, 1498, 1443

NMR (270MHz; $CDCl_3$) δ (ppm): 7.70(1H, d, J=15.5Hz), 7.10(1H, d, J=1.6Hz), 7.06(1H, dd, J=1.6, 8.0Hz), 6.84(1H, d, J=8.0Hz), 6.73(1H, d, J=15.5Hz), 6.02 (2H, s), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 1.38(3H, t, J=6.9Hz), 1.26 (3H, t, J=6.9Hz)

Example 17

(E)-8-[2-(1,4-Benzodioxan-6-yl)vinyl]-1,3-diethylxanthine (Compound 17)

Substantially the same procedure as in Example 1 was repeated using 2.85 g (14.4 mmol) of 5,6-diamino-1,3-diethyluracil and 2.70 g (13.1 mmol) of 3-(1,4-benzodioxan-6-yl)acrylic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.45 g (yield 51%) of Compound 17 as a pale yellow powder.

Melting Point: >300°C

Elemental Analysis: $C_{19}H_{20}N_4O_4$			
Calcd. (%):	C, 61.94;	H, 5.47;	N, 15.20
Found (%):	C, 61.97;	H, 5.62;	N, 15.07

IR (KBr) ν_{max} (cm^{-1}): 1682, 1637, 1511, 1310

NMR (270MHz; DMSO-d_6) δ (ppm): 7.51(1H, d, J=16.2Hz), 7.10-7.03(2H, m), 6.89(1H, d, J=7.9Hz), 6.87(1H, d, J=16.2Hz), 4.27(4H, s), 4.05(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 1.22(3H, t, J=6.9Hz), 1.13 (3H, t, J=6.9Hz)

Example 18

(E)-8-[2-(1,4-Benzodioxan-6-yl)vinyl]-1,3-diethyl-7-methylxanthine (Compound 18)

Substantially the same procedure as in Example 2 was repeated using 2.00 g (5.43 mmol) of Compound 17 obtained in Example 17 in place of Compound 1. Then, the resultant crude crystals were recrystallized from ethanol/isopropanol to give 1.58 g (yield 76%) of Compound 18 as yellow needles.

Melting Point: 233.1-233.6°C

Elemental Analysis: $C_{20}H_{22}N_4O_4$			
Calcd. (%):	C, 62.81;	H, 5.79;	N, 14.65
Found (%):	C, 62.55;	H, 5.80;	N, 14.60

IR (KBr) ν_{max} (cm^{-1}): 1689, 1654, 1509

NMR (270MHz; $CDCl_3$) δ (ppm): 7.67(1H, d, J=15.8Hz), 7.15-7.05(2H, m), 6.88(1H, d, J=8.3Hz), 6.75(1H, d, J=15.8Hz), 4.30(4H, s), 4.21(2H, q, J=6.9Hz), 4.08(2H, q, J=6.9Hz), 4.03(3H, s), 1.39(3H, t, J=6.9Hz), 1.35(3H, t, J=6.9Hz)

Example 19

(E)-8-(2,3,4-Trimethoxystyryl)theophylline (Compound 19)

Substantially the same procedure as in Example 1 was repeated using 5.00 g (29.4 mmol) of 5,6-diamino-1,3-dimethyluracil and 7.71 g (32.4 mmol) of 2,3,4-trimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from isopropanol/water to give 3.78 g (yield 35%) of Compound 19 as an ocher powder.

Melting Point: 264.8-266.1°C

Elemental Analysis: $C_{18}H_{20}N_4O_5$			
Calcd. (%):	C, 58.05;	H, 5.41;	N, 15.04
Found (%):	C, 58.28;	H, 5.38;	N, 15.20

IR (KBr) ν_{max} (cm^{-1}): 1697, 1651, 1505, 1297

NMR (270MHz; $CDCl_3$) δ (ppm): 12.78(1H, s), 7.91(1H, d, J=16.8Hz), 7.28(1H, d, J=9.4Hz), 7.13(1H, d, J=16.8Hz), 6.73(1H, d, J=9.4Hz), 3.95(3H, s), 3.92 (3H, s), 3.90(3H, s), 3.69(3H, s), 3.54(3H, s)

Example 20

(E)-8-(2,3,4-Trimethoxystyryl)caffeine (Compound 20)

Substantially the same procedure as in Example 2 was repeated using 2.00 g (5.38 mmol) of Compound 19 obtained in Example 19 in place of Compound 1. Then, the resultant crude crystals were recrystallized from cyclohexane/toluene to give 1.68 g (yield 81%) of Compound 20 as a pale yellow powder.

Melting Point: 186.7-187.9°C

Elemental Analysis: $C_{19}H_{22}N_4O_5$

Calcd. (%): C, 59.06; H, 5.74; N, 14.50

Found (%): C, 59.27; H, 5.72; N, 14.60

IR (KBr) ν_{max} (cm^{-1}): 1694, 1655, 1596, 1544, 1501, 1295

NMR (270MHz; $CDCl_3$) δ (ppm): 7.90(1H, d, J=16.3Hz), 7.28(1H, d, J=7.9Hz), 7.01(1H, d, J=16.3Hz), 6.72 (1H, d, J=7.9Hz), 4.04(3H, s), 3.97(3H, s), 3.91 (3H, s), 3.90(3H, s), 3.64(3H, s), 3.42(3H, s)

Example 21

(E)-8-(4-Methoxy-2,3-dimethylstyryl)theophylline (Compound 21)

Substantially the same procedure as in Example 1 was repeated using 1.74 g (10.2 mmol) of 5,6-diamino-1,3-dimethyluracil and 2.42 g (11.8 mmol) of 4-methoxy-2,3-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from acetonitrile to give 750 mg (yield 22%) of Compound 21 as a white powder.

Melting Point: >275°C

Elemental Analysis: $C_{18}H_{20}N_4O_3$			
Calcd. (%):	C, 63.51;	H, 5.92;	N, 16.46
Found (%):	C, 63.56;	H, 5.82;	N, 16.30

IR (KBr) ν_{max} (cm^{-1}): 1703, 1634, 1593

NMR (270MHz; DMSO-d_6) δ (ppm): 13.45(1H, s), 7.93(1H, d, J=16.2Hz), 7.53(1H, d, J=8.9Hz), 6.88(1H, d, J=8.9Hz), 6.79(1H, d, J=16.2Hz), 3.80(3H, s), 3.75 (3H, s), 3.25(3H, s), 2.32(3H, s), 2.12(3H, s)

Example 22

(E)-8-(4-Methoxy-2,3-dimethylstyryl)caffeine (Compound 22)

Substantially the same procedure as in Example 2 was repeated using 500 mg (1.47 mmol) of Compound 21 obtained in Example 21 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene to give 280 mg (yield 54%) of Compound 22 as a pale yellow powder.

Melting Point: >275°C

Elemental Analysis: $C_{19}H_{22}N_4O_3$			
Calcd. (%):	C, 64.39;	H, 6.25;	N, 15.80
Found (%):	C, 64.44;	H, 6.27;	N, 16.11

IR (KBr) ν_{max} (cm^{-1}): 1694, 1650, 1544, 1491, 1435

NMR (270MHz; $CDCl_3$) δ (ppm): 7.96(1H, d, J=15.5Hz), 7.73(1H, d, J=8.6Hz), 7.07(1H, d, J=15.5Hz), 6.90 (1H, d, J=8.6Hz), 4.02(3H, s), 3.82(3H, s), 3.48 (3H, s), 3.29(3H, s), 2.32(3H, s), 2.13(3H, s)

Example 23

(E)-8-(3,4-Methylenedioxystyryl)theophylline (Compound 23)

Substantially the same procedure as in Example 1 was repeated using 5.0 g (29.4 mmol) of 5,6-diamino-1,3-dimethyluracil and 6.78 g (35.3 mmol) of 3,4-methylenedioxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/water to give 1.20 g (yield 13%) of Compound 23 as a pale yellow powder.

Melting Point: >275°C

Elemental Analysis: $C_{16}H_{14}N_4O_4$			
Calcd. (%):	C, 58.99;	H, 4.32;	N, 17.16
Found (%):	C, 58.84;	H, 4.30;	N, 16.97

IR (KBr) ν_{max} (cm^{-1}): 1692, 1642, 1499

NMR (270MHz; DMSO-d_6) δ (ppm): 7.57(1H, d, J=16.1Hz), 7.09(1H, s), 7.07(1H, d, J=7.9Hz), 6.92(1H, d, J=7.9Hz), 6.88(1H, d, J=16.1Hz), 6.07(2H, s), 3.47 (3H, s), 3.30(3H, s)

Example 24

(E)-8-(3,4-Methylenedioxystyryl)caffein (Compound 24)

Substantially the same procedure as in Example 2 was repeated using 2.32 g (7.13 mmol) of Compound 23 obtained in Example 23 in place of Compound 1. Then, the resultant crude crystals were recrystallized from dioxane to give 1.54 g (yield 64%) of Compound 24 as yellow needles.

Melting Point: >300°C

Elemental Analysis: $C_{17}H_{16}N_4O_4$			
Calcd. (%):	C, 59.99;	H, 4.73;	N, 16.46
Found (%):	C, 59.98;	H, 4.66;	N, 16.38

IR (KBr) ν_{max} (cm^{-1}): 1702, 1663, 1545, 1506

NMR (270MHz; $CDCl_3$) δ (ppm): 7.72(1H, d, J=15.3Hz), 7.10(1H, d, J=1.5Hz), 7.06(1H, dd, J=1.5, 7.9Hz), 6.84(1H, d, J=7.9Hz), 6.73(1H, d, J=15.3Hz), 6.03 (2H, s), 4.05(3H, s), 3.63(3H, s), 3.42(3H, s)

Example 25

(E)-8-(2,3-Dimethoxystyryl)theophylline (Compound 25)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (14.7 mmol) of 5,6-diamino-1,3-dimethyluracil and 3.37 g (16.2 mmol) of 2,3-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.03 g (yield 41%) of Compound 25 as pale yellow needles.

Melting Point: 289.2-290.5°C

Elemental Analysis: $C_{17}H_{18}N_4O_4$			
Calcd. (%):	C, 59.64;	H, 5.29;	N, 16.36
Found (%):	C, 59.42;	H, 5.12;	N, 16.65

IR (KBr) ν_{max} (cm^{-1}): 1700, 1649, 1499, 1476, 1273

NMR (270MHz; DMSO-d_6) δ (ppm): 13.60(1H, brs), 7.84 (1H, d, J=16.8Hz), 7.26(1H, d, J=6.9Hz), 7.15-7.00 (3H, m), 3.83(3H, s), 3.79(3H, s), 3.48(3H, s), 3.26(3H, s)

Example 26

(E)-8-(2,3-Dimethoxystyryl)caffeine (Compound 26)

Substantially the same procedure as in Example 2 was repeated using 1.10 g (3.22 mmol) of Compound 25 obtained in Example 25 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene to give 570 mg (yield 50%) of Compound 26 as yellow needles.

Melting Point: 233.6-236.7°C

Elemental Analysis: $C_{18}H_{20}N_4O_4$			
Calcd. (%):	C, 60.66;	H, 5.65;	N, 15.72
Found (%):	C, 60.21;	H, 5.74;	N, 16.13

IR (KBr) ν_{max} (cm^{-1}): 1688, 1645, 1545, 1480

NMR (270MHz; DMSO-d_6) δ (ppm): 7.91(1H, d, J=16.0Hz), 7.52(1H, dd, J=1.7, 7.6Hz), 7.32(1H, d, J=16.0Hz), 7.10-7.05(2H, m), 4.03(3H, s), 3.84(3H, s), 3.79 (3H, s), 3.48(3H, s), 3.24(3H, s)

Example 27

(E)-8-(2,4-Dimethoxystyryl)theophylline (Compound 27)

Substantially the same procedure as in Example 1 was repeated using 1.0 g (5.88 mmol) of 5,6-diamino-1,3-dimethyluracil and 1.35 g (6.48 mmol) of 2,4-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide to give 221 mg (yield 11%) of Compound 27 as pale yellow grains.

Melting Point: >280°C

Elemental Analysis: $C_{17}H_{18}N_4O_4$			
Calcd. (%):	C, 59.64;	H, 5.29;	N, 16.36
Found (%):	C, 59.51;	H, 5.34;	N, 16.58

IR (KBr) ν_{max} (cm^{-1}): 1705, 1650, 1607, 1505

NMR (270MHz; DMSO-d_6) δ (ppm): 13.40(1H, brs), 7.78 (1H, d, J=16.5Hz), 7.53(1H, d, J=8.3Hz), 6.93(1H, d, J=16.5Hz), 6.63(1H, d, J=2.3Hz), 6.60(1H, dd, J=2.3, 8.3Hz), 3.89(3H, s), 3.82(3H, s), 3.47(3H, s), 3.25(3H, s)

Example 28

(E)-8-(2,4-Dimethoxystyryl)caffeine (Compound 28)

Substantially the same procedure as in Example 2 was repeated using 700 mg (2.05 mmol) of Compound 27 obtained in Example 27 in place of Compound 1. Then, the resultant crude crystals were recrystallized from dioxane to give 621 mg (yield 85%) of Compound 28 as yellow needles.

Melting Point: 241.5-242.1°C

Elemental Analysis: $C_{18}H_{20}N_4O_4$			
Calcd. (%):	C, 60.66;	H, 5.65;	N, 15.72
Found (%):	C, 60.49;	H, 5.61;	N, 15.69

IR (KBr) ν_{max} (cm^{-1}): 1685, 1650, 1602, 1434

NMR (270MHz; $CDCl_3$) δ (ppm): 7.95(1H, d, J=15.8Hz), 7.48(1H, d, J=8.6Hz), 6.98(1H, d, J=15.8Hz), 6.54 (1H, dd, J=2.3, 8.6Hz), 6.49(1H, d, J=2.3Hz), 4.03 (3H, s), 3.92(3H, s), 3.86(3H, s), 3.64(3H, s), 3.42(3H, s)

Example 29

(E)-8-(4-Methoxy-2,5-dimethylstyryl)theophylline (Compound 29)

Substantially the same procedure as in Example 1 was repeated using 1.0 g (5.88 mmol) of 5,6-diamino-1,3-dimethyluracil and 1.33 g (6.45 mmol) of 4-methoxy-2,5-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide to give 393 mg (yield 20%) of Compound 29 as pale yellow grains.

Melting Point: >280°C

Elemental Analysis: $C_{18}H_{20}N_4O_3$			
Calcd. (%):	C, 63.51;	H, 5.92;	N, 16.46
Found (%):	C, 63.59;	H, 6.10;	N, 16.23

IR (KBr) ν_{max} (cm^{-1}): 1703, 1648, 1509, 1260

NMR (270MHz; DMSO-d_6) δ (ppm): 13.48(1H, brs), 7.81 (1H, d, J=16.2Hz), 7.50(1H, s), 6.82(1H, d, J=16.2Hz), 6.81(1H, s), 3.81(3H, s), 3.46(3H, s), 3.25(3H, s), 2.40(3H, s), 2.14(3H, s)

Example 30

(E)-8-(4-Methoxy-2,5-dimethylstyryl)caffeine (Compound 30)

Substantially the same procedure as in Example 2 was repeated using 300 mg (0.88 mmol) of Compound 29 obtained in Example 29 in place of Compound 1. Then, the resultant crude crystals were recrystallized from dioxane to give 211 mg (yield 68%) of Compound 30 as yellow needles.

Melting Point: >280°C

MS-EI m/e: 354(M^+), 339(M^+-CH_3)

IR (KBr) ν_{max} (cm^{-1}): 1692, 1653, 1508

NMR (270MHz; $CDCl_3$) δ (ppm): 8.00(1H, d, J=15.3Hz), 7.42(1H, s), 6.72(1H, d, J=15.3Hz), 6.66(1H,

s), 4.06(3H, s), 3.86(3H, s), 3.64(3H, s), 3.42(3H, s), 2.49(3H, s), 2.23(3H, s)

Example 31

(E)-8-(2,4-Dimethoxy-3-methylstyryl)theophylline (Compound 31)

Substantially the same procedure as in Example 1 was repeated using 1.0 g (5.88 mmol) of 5,6-diamino-1,3-dimethyluracil and 1.44 g (6.45 mmol) of 2,4-dimethoxy-3-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 581 mg (yield 28%) of Compound 31 as pale yellow needles.

Melting Point: >280°C

Elemental Analysis: $C_{18}H_{20}N_4O_4$			
Calcd. (%):	C, 60.67;	H, 5.65;	N, 15.72
Found (%):	C, 60.34;	H, 5.77;	N, 15.64

IR (KBr) ν_{max} (cm^{-1}): 1695, 1653, 1499, 1270

NMR (270MHz; DMSO-d_6) δ (ppm): 13.52(1H, brs), 7.75 (1H, d, J=16.2Hz), 7.55(1H, d, J=8.3Hz), 6.96(1H, d, J=16.2Hz), 6.84(1H, d, J=8.3Hz), 3.83(3H, s), 3.70(3H, s), 3.47(3H, s), 3.25(3H, s), 2.09(3H, s)

Example 32

(E)-8-(2,4-Dimethoxy-3-methylstyryl)caffeine (Compound 32)

Substantially the same procedure as in Example 2 was repeated using 300 mg (0.84 mmol) of Compound 31 obtained in Example 31 in place of Compound 1. Then, the resultant crude crystals were recrystallized from methylene chloride/diethyl ether to give 239 mg (yield 77%) of Compound 32 as white needles.

Melting Point: 252.7-253.5°C

Elemental Analysis: $C_{19}H_{22}N_4O_4$			
Calcd. (%):	C, 61.61;	H, 5.98;	N, 15.13
Found (%):	C, 61.40;	H, 6.06;	N, 15.17

IR (KBr) ν_{max} (cm^{-1}): 1692, 1651, 1505

NMR (270MHz; $CDCl_3$) δ (ppm): 7.92(1H, d, J=15.8Hz), 7.42(1H, d, J=8.9Hz), 6.99(1H, d, J=15.8Hz), 6.70 (1H, d, J=8.9Hz), 4.04(3H, s), 3.88(3H, s), 3.78 (3H, s), 3.64(3H, s), 3.42(3H, s), 2.19(3H, s)

Example 33

(E)-8-(2,5-Dimethylstyryl)-1,3-diethylxanthine (Compound 33)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.20 g (18.2 mmol) of 2,5-dimethylcinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/toluene to give 2.56 g (yield 50%) of Compound 33 as white needles.

Melting Point: 281.8-282.5°C

Elemental Analysis: $C_{19}H_{22}N_4O_2 \cdot 0.5H_2O$			
Calcd. (%):	C, 66.46;	H, 6.97;	N, 15.50
Found (%):	C, 66.77;	H, 6.82;	N, 15.72

IR (KBr) ν_{max} (cm^{-1}): 1706, 1639, 1503

NMR (270MHz; DMSO-d_6) δ (ppm): 7.84(1H, d, J=16.3Hz), 7.53(1H, s), 7.13(1H, d, J=7.4Hz), 7.06(1H, d, J=7.4Hz), 7.00(1H, d, J=16.3Hz), 4.06(2H, q, J=7.1Hz), 3.94(2H, q, J=7.1Hz), 2.37(3H, s), 2.30 (3H, s), 1.26(3H, t, J=7.1Hz), 1.14(3H, t, J=7.1Hz)

Example 34

(E)-8-(2,5-Dimethylstyryl)-1,3-diethyl-7-methylxanthine (Compound 34)

Substantially the same procedure as in Example 2 was repeated using 2.00 g (5.92 mmol) of Compound 33 obtained in Example 33 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.29 g (yield 62%) of Compound 34 as white needles.

Melting Point: 190.3-190.7°C

Elemental Analysis: $C_{20}H_{24}N_4O_2$			
Calcd. (%):	C, 68.16;	H, 6.86;	N, 15.89
Found (%):	C, 68.15;	H, 7.02;	N, 15.65

IR (KBr) ν_{max} (cm^{-1}): 1698, 1657

NMR (270MHz; $CDCl_3$) δ (ppm): 7.86(1H, d, J=15.8Hz), 7.71(1H, s), 7.23(1H, d, J=15.8Hz), 7.15(1H, d, J=7.9Hz), 7.09(1H, d, J=7.9Hz), 4.11-4.04(2H, m), 4.04(3H, s), 3.92(2H, q, J=6.9Hz), 2.37(3H, s), 2.32(3H, s), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Example 35

(E)-8-(4-Ethoxystyryl)-1,3-diethylxanthine (Compound 35)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.20 g (16.7 mmol) of 4-ethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 2.97 g (yield 55%) of Compound 35 as pale yellow needles.

Melting Point: 296.7-298.6°C

Elemental Analysis: $C_{19}H_{22}N_4O_3$			
Calcd. (%):	C, 64.39;	H, 6.25;	N, 15.81
Found (%):	C, 64.54;	H, 6.52;	N, 15.80

IR (KBr) ν_{max} (cm^{-1}): 1695, 1647, 1516, 1250

NMR (270MHz; DMSO-d_6) δ (ppm): 13.36(1H, brs), 7.59 (1H, d, J=16.2Hz), 7.55(2H, d, J=8.6Hz), 6.96(2H, d, J=8.6Hz), 6.88(1H, d, J=16.2Hz), 4.11-4.04(4H, m), 3.94(2H, q, J=6.9Hz), 1.34(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Example 36

(E)-8-(4-Ethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 36)

Substantially the same procedure as in Example 2 was repeated using 1.60 g (4.52 mmol) of Compound 35 obtained in Example 35 in place of Compound 1. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 1.47 g (yield 88%) of Compound 36 as pale green needles.

Melting Point: 185.3-185.7°C

Elemental Analysis: $C_{20}H_{24}N_4O_3$			
Calcd. (%):	C, 65.20;	H, 6.56;	N, 15.21
Found (%):	C, 65.28;	H, 6.85;	N, 15.18

IR (KBr) ν_{max} (cm^{-1}): 1693, 1666, 1515, 1248

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.52(2H, d, J=8.6Hz), 6.92(2H, d, J=8.6Hz), 6.77 (1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.12-4.01 (4H, m), 4.04(3H, s), 1.44(3H, t, J=6.9Hz), 1.38 (3H, t, J=7.6Hz), 1.26(3H, t, J=6.9Hz)

Example 37

(E)-1,3-Diethyl-8-(4-propoxystyryl)xanthine (Compound 37)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.43 g (16.6 mmol) of 4-propoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.02 g (yield 54%) of Compound 37 as pale yellow needles.

Melting Point: >270°C

Elemental Analysis: $C_{20}H_{24}N_4O_3$			
Calcd. (%):	C, 65.20;	H, 6.56;	N, 15.21
Found (%):	C, 64.91;	H, 6.79;	N, 15.14

IR (KBr) ν_{max} (cm^{-1}): 1695, 1656, 1515, 1250

NMR (270MHz; DMSO-d_6) δ (ppm): 13.38(1H, brs), 7.59 (1H, d, J=16.5Hz), 7.55(2H, d, J=8.6Hz), 6.97(2H, d, J=8.6Hz), 6.87(1H, d, J=16.5Hz), 4.07(2H, q, J=7.3Hz), 4.00-3.90(4H, m), 1.81-1.67(2H, m), 1.26 (3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz), 0.98(3H, t, J=7.3Hz)

Example 38

(E)-1,3-Diethyl-7-methyl-8-(4-propoxystyryl)xanthine (Compound 38)

Substantially the same procedure as in Example 2 was repeated using 1.70 g (4.61 mmol) of Compound 37 obtained in Example 37 in place of Compound 1. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.37 g (yield 78%) of Compound 38 as pale yellow needles.

Melting Point: 155.7-156.5°C

Elemental Analysis: $C_{21}H_{26}N_4O_3$			
Calcd. (%):	C, 65.92;	H, 6.85;	N, 14.65
Found (%):	C, 65.72;	H, 7.05;	N, 14.59

IR (KBr) ν_{max} (cm^{-1}): 1696, 1665, 1513, 1246

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.52(2H, d, J=8.6Hz), 6.92(2H, d, J=8.6Hz), 6.77 (1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 3.97(2H, t, J=6.6Hz), 1.90-1.77(2H, m), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.05(3H, t, J=7.3Hz)

Example 39

(E)-1,3-Diethyl-8-(3-methoxystyryl)xanthine (Compound 39)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.48 g (13.9 mmol) of 3-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide/water to give 2.10 g (yield 49%) of Compound 39 as a white powder.

Melting Point: 270.6-272.5°C

Elemental Analysis: $C_{18}H_{20}N_4O_3$

Calcd. (%): C, 63.52; H, 5.92; N, 16.46

Found (%): C, 63.20; H, 6.01; N, 16.34

IR (KBr) ν_{max} (cm^{-1}): 1686, 1634, 1500

NMR (270MHz; DMSO-d_6) δ (ppm): 7.61(1H, d, J=16.4Hz), 7.34(1H, t, J=7.9Hz), 7.20-7.18(2H, m), 7.07(1H, d, J=16.4Hz), 6.92(1H, d, J=8.6Hz), 4.06(2H, q, J=7.0Hz), 3.94(2H, q, J=6.8Hz), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=6.8Hz)

Example 40

(E)-1,3-Diethyl-8-(3-methoxystyryl)-7-methylxanthine (Compound 40)

Substantially the same procedure as in Example 2 was repeated using 1.70 g (5.00 mmol) of Compound 39 obtained in Example 39 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.10 g (yield 62%) of Compound 40 as pale yellow needles.

Melting Point: 153.4-154.8°C

Elemental Analysis: $C_{19}H_{22}N_4O_3$			
Calcd. (%):	C, 64.39;	H, 6.26;	N, 15.81
Found (%):	C, 64.34;	H, 6.38;	N, 15.82

IR (KBr) ν_{max} (cm^{-1}): 1692, 1656, 1541

NMR (270MHz; DMSO-d_6) δ (ppm): 7.64(1H, d, J=15.8Hz), 7.40-7.30(4H, m), 6.97-6.92(1H, m), 4.31-4.05(2H, m), 4.05(3H, s), 3.92(2H, q, J=7.0Hz), 1.26(3H, t, J=7.1Hz), 1.13(3H, t, J=7.0Hz)

Example 41

(E)-8-(4-Butoxystyryl)-1,3-diethylxanthine (Compound 41)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.67 g (16.7 mmol) of 4-butoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.04 g (yield 53%) of Compound 41 as pale yellow needles.

Melting Point: 257.9-261.3°C

Elemental Analysis: $C_{21}H_{26}N_4O_3$			
Calcd. (%):	C, 65.95;	H, 6.85;	N, 14.65
Found (%):	C, 65.90;	H, 7.21;	N, 14.60

IR (KBr) ν_{max} (cm^{-1}): 1695, 1645, 1515, 1248

NMR (270MHz; DMSO-d_6) δ (ppm): 13.32(1H, brs), 7.59 (1H, d, J=16.5Hz), 7.55(2H, d, J=8.9Hz), 6.97(2H, d, J=8.9Hz), 6.87(1H, d, J=16.5Hz), 4.10-3.90(6H, m), 1.76-1.66(2H, m), 1.51-1.40(2H, m), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz), 0.94(3H, t, J=7.3Hz)

Example 42

(E)-8-(4-Butoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 42)

Substantially the same procedure as in Example 2 was repeated using 1.50 g (3.92 mmol) of Compound 41 obtained in Example 41 in place of Compound 1. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 982 mg (yield 63%) of Compound 42 as pale yellow needles.

Melting Point: 123.4-123.6°C

Elemental Analysis: $C_{22}H_{28}N_4O_3$			
Calcd. (%):	C, 66.65;	H, 7.11;	N, 14.13
Found (%):	C, 66.81;	H, 7.31;	N, 14.01

IR (KBr) ν_{max} (cm^{-1}): 1693, 1665, 1513, 1251

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.52(2H, d, J=8.9Hz), 6.92(2H, d, J=8.9Hz), 6.76 (1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 4.02(2H, q, J=6.6Hz), 1.84-1.74(2H, m), 1.58-1.44(2H, m), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 0.99(3H, t, J=7.3Hz)

Example 43

(E)-1,3-Diethyl-8-(4-methylstyryl)xanthine (Compound 43)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.70 g (16.7 mmol) of 4-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 2.64 g (yield 54%) of Compound 43 as pale yellow needles.

Melting Point: >280°C

Elemental Analysis: $C_{18}H_{20}N_4O_2$			
Calcd. (%):	C, 66.65;	H, 6.21;	N, 17.27
Found (%):	C, 66.53;	H, 6.27;	N, 17.14

IR (KBr) ν_{max} (cm^{-1}): 1692, 1644, 1518, 1490

NMR (270MHz; DMSO-d_6) δ (ppm): 13.53(1H, brs), 7.62 (1H, d, J=16.5Hz), 7.52(2H, d, J=7.9Hz), 7.24(2H, d, J=7.9Hz), 6.98(1H, d, J=16.5Hz), 4.07(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 2.33(3H, s), 1.26 (3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Example 44

(E)-1,3-Diethyl-7-methyl-8-(4-methylstyryl)xanthine (Compound 44)

Substantially the same procedure as in Example 2 was repeated using 1.50 g (4.62 mmol) of Compound 43 obtained in Example 43 in place of Compound 1. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.39 g (yield 89%) of Compound 44 as yellow needles.

Melting Point: 170.8-171.5°C

Elemental Analysis: $C_{19}H_{22}N_4O_2$			
Calcd. (%):	C, 67.44;	H, 6.55;	N, 16.56
Found (%):	C, 67.58;	H, 6.65;	N, 16.68

IR (KBr) ν_{max} (cm^{-1}): 1687, 1650, 1542, 1516

NMR (270MHz; $CDCl_3$) δ (ppm): 7.77(1H, d, J=15.8Hz), 7.48(2H, d, J=8.3Hz), 7.21(2H, d, J=8.3Hz), 6.87 (1H, d, J=15.8Hz), 4.22(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.05(3H, s), 2.39(3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Example 45

(E)-1,3-Diethyl-8-(2-methoxystyryl)xanthine (Compound 45)

Substantially the same procedure as in Example 1 was repeated using 2.5 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.48 g (13.9 mmol) of 2-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 990 mg (yield 24%) of Compound 45 as yellow grains.

Melting Point: >270°C

Elemental Analysis: $C_{18}H_{20}N_4O_3$			
Calcd. (%):	C, 63.52;	H, 5.92;	N, 16.46
Found (%):	C, 63.28;	H, 5.86;	N, 16.43

IR (KBr) ν_{max} (cm^{-1}): 1694, 1640, 1501

NMR (270MHz; DMSO-d_6) δ (ppm): 7.85(1H, d, J=16.8Hz), 7.62(1H, d, J=7.6Hz), 7.34(1H, t, J=7.6Hz), 7.11-6.98(3H, m), 4.07(2H, q, J=7.0Hz), 3.97-3.89(2H, m), 3.89(3H, s), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=6.9Hz)

Exampl 46

(E)-1,3-Diethyl-8-(2-methoxystyryl)-7-methylxanthin (Compound 46)

Substantially the same procedure as in Example 2 was repeated using 1.5 g (4.41 mmol) of Compound 45 obtained in Example 45 in plac of Compound 1. Then, the resultant crud crystals wer recrystallized from

ethanol/water to give 800 mg (yield 51%) of Compound 46 as yellow needles.

Melting Point: 189.6-190.0°C

Elemental Analysis: $C_{19}H_{22}N_4O_3$			
Calcd. (%):	C, 64.39;	H, 6.26;	N, 15.81
Found (%):	C, 64.18;	H, 6.25;	N, 15.77

IR (KBr) ν_{max} (cm^{-1}): 1697, 1649

NMR (270MHz; DMSO-d_6) δ (ppm): 7.94(1H, d, J=15.8Hz), 7.88(1H, dd, J=7.9, 1.5Hz), 7.41-7.34(1H, m), 7.31 (1H, d, J=15.8Hz), 7.10(1H, d, J=7.9Hz), 7.02(1H, t, J=7.4Hz), 4.11-4.02(2H, m), 4.02(3H, s), 3.96-3.90(2H, m), 3.90(3H, s), 1.29(3H, t, J=7.2Hz), 1.13(3H, t, J=7.2Hz)

Example 47

(E)-1,3-Diethyl-8-(4-methoxy-3-methylstyryl)xanthine (Compound 47)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.00 g (13.9 mmol) of 4-methoxy-3-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylsulfoxide/water to give 1.70 g (yield 36%) of Compound 47 as white flocculent precipitates.

Melting Point: >270°C

Elemental Analysis: $C_{19}H_{22}N_4O_3$			
Calcd. (%):	C, 64.39;	H, 6.23;	N, 15.81
Found (%):	C, 64.05;	H, 6.34;	N, 15.74

IR (KBr) ν_{max} (cm^{-1}): 1689, 1644, 1510, 1459

NMR (270MHz; DMSO-d_6) δ (ppm): 7.56(1H, d, J=16.3Hz), 7.45(1H, s), 7.44(1H, d, J=8.2Hz), 6.98(1H, d, J=8.2Hz), 6.87(1H, d, J=16.3Hz), 4.06(2H, q, J=7.1Hz), 3.93(2H, q, J=7.0Hz), 3.82(3H, s), 2.18 (3H, s), 1.25(3H, t, J=7.1Hz), 1.13(3H, t, J=7.0Hz)

Example 48

(E)-1,3-Diethyl-8-(4-methoxy-3-methylstyryl)-7-methylxanthine (Compound 48)

Substantially the same procedure as in Example 2 was repeated using 1.27 g (3.36 mmol) of Compound 47 obtained in Example 47 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.01 g (yield 82%) of Compound 48 as yellow needles.

Melting Point: 176.5-177.6°C

Elemental Analysis: $C_{20}H_{24}N_4O_3$			
Calcd. (%):	C, 65.20;	H, 6.57;	N, 15.21
Found (%):	C, 65.22;	H, 6.75;	N, 15.22

IR (KBr) ν_{max} (cm^{-1}): 1687, 1648, 1542, 1505, 1434

NMR (270MHz; DMSO-d_6) δ (ppm): 7.65(1H, s), 7.58(1H, d, J=15.8Hz), 7.57-7.53(1H, m), 7.16(1H, d, J=15.8Hz), 6.97(1H, d, J=8.9Hz) , 4.10-4.01(2H, m), 4.01(3H, s), 3.91(2H, q, J=6.9Hz), 3.88(3H, s), 2.19(3H, s), 1.25(3H, t, J=6.9Hz), 1.12(3H, t, J=6.9Hz)

Exampl 49

(E)-8-(2-Bromo-4,5-methyl nedioxystyryl)-1,3-di thylxanthin (Compound 95)

Substantially the sam procedure as in Exampl 1 was rep ated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-di thyluracil and 3.77 g (13.9 mmol) of 2-bromo-4,5-methyl nedioxycinnamic acid. Then, the resultant

crude crystals were recrystallized from dimethylsulfoxide/water to give 2.01 g (yield 38%) of Compound 95 as a yellow powder.

Melting Point: >270°C

Elemental Analysis: $C_{18}H_{17}BrN_4O_4 \cdot 0.25H_2O$			
Calcd. (%):	C, 49.39;	H, 4.03;	N, 12.80
Found (%):	C, 49.42;	H, 3.75;	N, 12.67

IR (KBr) ν_{max} (cm^{-1}): 1691, 1651, 1497

NMR (270MHz; DMSO-d_6) δ (ppm): 7.78(1H, d, J=8.2Hz), 7.48(1H, s), 7.30(1H, s), 6.97(1H, d, J=8.2Hz), 6.13(2H, s), 4.05(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 1.24(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Example 50

(E)-8-(2-Bromo-4,5-methylenedioxystyryl)-1,3-diethyl-7-methylxanthine (Compound 96)

Substantially the same procedure as in Example 2 was repeated using 2.20 g (5.08 mmol) of Compound 95 obtained in Example 49 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.17 g (yield 52%) of Compound 96 as a pale yellow powder.

Melting Point: 255.1-256.0°C

Elemental Analysis: $C_{19}H_{19}BrN_4O_4$			
Calcd. (%):	C, 51.02;	H, 4.28;	N, 12.53
Found (%):	C, 50.94;	H, 4.15;	N, 12.39

IR (KBr) ν_{max} (cm^{-1}): 1693, 1651

NMR (270MHz; DMSO-d_6) δ (ppm): 7.87(1H, d, J=15.8Hz), 7.77(1H, s), 7.30(1H, d, J=15.8Hz), 7.32(1H, s), 6.15(2H, s), 4.10-4.03(2H, m), 4.03(3H, s), 3.92 (2H, q, J=6.8Hz), 1.26(3H, t, J=7.2Hz), 1.13(3H, t, J=6.8Hz)

Example 51

(E)-1,3-Diethyl-8-(3-methoxy-4,5-methylenedioxystyryl)xanthine (Compound 106)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.31 g (14.9 mmol) of 3-methoxy-4,5-methylenedioxycinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 600 mg (yield 53%) of Compound 106 as a white powder.

Melting Point: >270°C

Elemental Analysis: $C_{19}H_{20}N_4O_5$			
Calcd. (%):	C, 59.37;	H, 5.24;	N, 14.58
Found (%):	C, 59.41;	H, 5.26;	N, 14.66

IR (KBr) ν_{max} (cm^{-1}): 1689, 1654, 1640, 1506

NMR (270MHz; DMSO-d_6) δ (ppm): 7.54(1H, d, J=16.6Hz), 6.94(2H, s), 6.93(1H, d, J=16.6Hz), 6.04(2H, s), 4.05(2H, q, J=6.9Hz), 3.97-3.88(2H, m), 3.88(3H, s), 1.25(3H, t, J=7.2Hz), 1.13(3H, t, J=7.2Hz)

Example 52

(E)-1,3-Di thyl-8-(3-methoxy-4,5-methylenedioxystyryl)-7-methylxanthin (Compound 107)

Substantially the same procedure as in Example 2 was repeated using 2.00 g (5.20 mmol) of Compound 106 obtained in Example 51 in place of Compound 1. Then, the resultant crude crystals were recrystallized from 2-propanol to give 730 mg (yi ld 35%) of Compound 107 as a yellow powd r.

Melting Point: 201.5-202.3°C

Elem ntal Analysis: $C_{20}H_{22}N_4O_5$			
Calcd. (%):	C, 60.29;	H, 5.57;	N, 14.06
Found (%):	C, 60.18;	H, 5.72;	N, 13.98

IR (KBr) ν_{max} (cm^{-1}): 1694, 1650, 1543, 1512, 1433

NMR (270MHz; DMSO-d_6) δ (ppm): 7.58(1H, d, J=15.8Hz), 7.23(1H, d, J=15.8Hz), 7.20(1H, d, J=1.0Hz), 7.09 (1H, d, J=1.0Hz), 6.05(2H, s), 4.09-4.02(2H, m), 4.02(3H, s), 3.94-3.89(2H, m), 3.89(3H, s), 1.25 (3H, t, J=7.2Hz), 1.13(3H, t, J=6.9Hz)

Example 53 Tablets

Tablets having the following composition were prepared in a conventional manner.

Composition of One Tablet	
Compound 2	20 mg
Lactose	143.4mg
Potato Starch	30 mg
Hydroxypropylcellulose	6 mg
Magnesium Stearate	0.6mg
	200 mg

Example 54 Fine Granules

Fine granules having the following composition were prepared in a conventional manner.

Composition of One Pack of Fine Granules	
Compound 107	20 mg
Lactose	655 mg
Corn Starch	285 mg
Hydroxypropylcellulose	40 mg
	1,000 mg

Example 55 Capsules

Capsules having the following composition were prepared in a conventional manner.

Composition of One Capsule	
Compound 8	20 mg
Avicel	99.5mg
Magn sium Stearat	0.5mg
	120 mg

Example 56 Injections

Injections having the following composition were prepared in a conventional manner.

Composition of One Injection Vial	
Compound 10	2 mg
Purified Soybean Oil	200 mg
Purified Egg Yolk Lecithin	24 mg
Glycerine for Injection	50 mg
Distilled Water for Injection	1.72 ml
	2.00 ml

Example 57 Syrup Preparations

Syrup Preparations having the following composition were prepared in a conventional manner.

Composition of One Syrup Preparation	
Compound 14	20 mg
Refined Sugar	30 mg
Ethyl p-Hydroxybenzoate	40 mg
Propyl p-Hydroxybenzoate	10 mg
Strawberry Flavor	0.1 ml
Water	99.8 ml
	100 ml

Reference Example 1

(E)-8-(2-Chloro-3,4-dimethoxystyryl)-1,3-diethylxanthine (Compound 49)

Substantially the same procedure as in Example 1 was repeated using 2.00 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.94 g (12.1 mmol) of 2-chloro-3,4-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 2.19 g (yield 54%) of Compound 49 as pale yellow needles.

Melting Point: 278.0-280.9°C

Elemental Analysis: $C_{19}H_{21}ClN_4O_4$			
Calcd. (%):	C, 56.36;	H, 5.22;	N, 13.83
Found (%):	C, 56.13;	H, 5.21;	N, 13.67

IR (KBr) ν_{max} (cm^{-1}): 1705, 1642, 1499

NMR (270MHz; DMSO-d_6) δ (ppm): 7.88(1H, d, J=16.3Hz), 7.64 (1H, d, J=8.9Hz), 7.13(1H, d, J=8.9Hz), 7.00 (1H, d, J=16.3Hz), 4.06(2H, q, J=7.1Hz), 3.98-3.88 (2H, m), 3.88(3H, s), 3.77(3H, s), 1.26(3H, t, J=7.1Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 2

(E)-8-(2-Chloro-3,4-dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 50)

Substantially the same procedure as in Example 2 was repeated using 1.80 g (4.45 mmol) of Compound 49 obtained in Reference Example 1 in place of Compound 1. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 1.20 g (yield 64%) of Compound 50 as yellow needles.

Melting Point: 204.6-205.4°C

Elemental Analysis: $C_{20}H_{23}ClN_4O_4$			
Calcd. (%):	C, 57.34;	H, 5.53;	N, 13.37
Found (%):	C, 57.46;	H, 5.67;	N, 13.10

IR (KBr) ν_{max} (cm^{-1}): 1696, 1657, 1496, 1439, 1292

NMR (270MHz; DMSO-d_6) δ (ppm): 7.92(1H, d, J=15.8Hz), 7.86(1H, d, J=8.9Hz), 7.29(1H, d, J=15.8Hz), 7.16 (1H, d, J=8.9Hz), 4.11-4.03(2H, m), 4.03(3H, s), 3.96-3.90(2H, m), 3.90(3H, s), 3.77(3H, s), 1.26 (3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 3

(E)-8-(2-Chloro-3,4-dimethoxystyryl)theophylline (Compound 51)

2-Chloro-3,4-dimethoxycinnamic acid (3.93 g, 16.2 mmol) was dissolved in 57 ml of pyridine. To the solution was added 1.26 ml (17.6 mmol) of thionyl chloride under ice cooling, and the mixture was stirred at 60°C for 1.5 hours. Methylene chloride (58 ml) containing 2.50g (14.7 mmol) of 5,6-diamino-1,3-dimethyluracil was added dropwise to the solution under ice cooling, and the reaction solution was stirred at room temperature for further 40 minutes. The deposited crystals were collected by filtration and the obtained crude crystals were dissolved in a mixture of 68 ml of an aqueous 2N sodium hydroxide solution, 68 ml of dioxane, and 34 ml of water, followed by heating under reflux for 30 minutes. After cooling, the solution was neutralized with a concentrated aqueous solution of hydrochloric acid, and the deposited crystals were collected by filtration. The collected crystals were washed with water, dried, and recrystallized from dimethylformamide/ water to give 1.55 g (yield 30%) of Compound 51 as pale yellow needles.

Melting Point: 241.6-242.6°C

Elemental Analysis: $C_{17}H_{17}ClN_4O_4$			
Calcd. (%):	C, 54.18;	H, 4.54;	N, 14.86
Found (%):	C, 54.31;	H, 4.54;	N, 14.43

IR (KBr) ν_{max} (cm^{-1}): 1704, 1653, 1496, 1300

NMR (270MHz; DMSO-d_6) δ (ppm): 7.88(1H, d, J=16.2Hz), 7.62(1H, d, J=8.9Hz), 7.13(1H, d, J=8.9Hz), 6.97 (1H, d, J=16.2Hz), 3.88(3H, s), 3.77(3H, s), 3.47 (3H, s), 3.25(3H, s)

Reference Example 4

(E)-8-(2-Chloro-3,4-dimethoxystyryl)caffeine (Compound 52)

Substantially the same procedure as in Example 2 was repeated using 1.0 g (2.66 mmol) of Compound 51 obtained in Reference Example 3 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene to give 840 mg (yield 81%) of Compound 52 as a yellow powder.

Melting Point: 284.6-288.0°C

Elemental Analysis: $C_{18}H_{19}ClN_4O_4$			
Calcd. (%):	C, 55.31;	H, 4.59;	N, 14.33
Found (%):	C, 55.40;	H, 4.83;	N, 14.09

IR (KBr) ν_{max} (cm^{-1}): 1688, 1650, 1493, 1290

NMR (270MHz; $CDCl_3$) δ (ppm): 8.10(1H, d, J=15.8Hz), 7.43(1H, d, J=8.8Hz), 6.88(1H, d, J=8.8Hz), 6.83 (1H, d, J=15.8Hz), 4.06(3H, s), 3.93(3H, s), 3.90 (3H, s), 3.64(3H, s), 3.42(3H, s)

Reference Example 5

(E)-8-(3,4-Difluorostyryl)-1,3-diethylxanthine (Compound 53)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.79 g (15.2 mmol) of 3,4-difluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.12 g (yield 49%) of Compound 53 as gray plates.

Melting Point: >300°C

Elemental Analysis: $C_{17}H_{16}F_2N_4O_2$			
Calcd. (%):	C, 58.95;	H, 4.65;	N, 16.17
Found (%):	C, 59.25;	H, 4.59;	N, 16.42

IR (KBr) ν_{max} (cm^{-1}): 1688, 1640, 1519

NMR (270MHz; DMSO-d_6) δ (ppm): 7.78(1H, dd, J=11.4, 7.1Hz), 7.60(1H, d, J=16.3Hz), 7.50-7.45(2H, m), 7.07(1H, d, J=16.3Hz), 4.06(2H, q, J=7.0Hz), 3.94 (2H, q, J=7.1Hz), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=7.1Hz)

Reference Example 6

(E)-8-(3,4-Difluorostyryl)-1,3-diethyl-7-methylxanthine (Compound 54)

Substantially the same procedure as in Example 2 was repeated using 1.70 g (4.91 mmol) of Compound 53 obtained in Reference Example 5 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.29 g (yield 73%) of Compound 54 as yellow needles.

Melting Point: 208.5-210.8°C

Elemental Analysis: $C_{18}H_{18}F_2N_4O_2$			
Calcd. (%):	C, 59.99;	H, 5.03;	N, 15.54
Found (%):	C, 60.09;	H, 5.04;	N, 15.19

IR (KBr) ν_{max} (cm^{-1}): 1688, 1652, 1545, 1520, 1441

NMR (270MHz; DMSO-d_6) δ (ppm): 8.02(1H, ddd, J=12.4, 7.7, 2.0Hz), 7.65-7.60(1H, m), 7.61(1H, d, J=15.8Hz), 7.54-7.43(1H, m), 7.40(1H, d, J=15.8Hz), 4.08-4.04(2H, m), 4.04(3H, s), 3.92(2H, q, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 7

(E)-8-(3-Bromo-4-methoxystyryl)-1,3-diethylxanthine (Compound 55)

Substantially the same procedure as in Example 1 was repeated using 2.00 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.72 g (10.6 mmol) of 3-bromo-4-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 726 mg (yield 17%) of Compound 55 as pale brown needles.

Melting Point: >280°C

Elemental Analysis: $C_{18}H_{19}BrN_4O_3$			
Calcd. (%):	C, 51.57;	H, 4.57;	N, 13.36
Found (%):	C, 51.33;	H, 4.56;	N, 13.17

IR (KBr) ν_{max} (cm^{-1}): 1694, 1648, 1506, 1281, 1260

NMR (270MHz; DMSO-d_6) δ (ppm): 13.52(1H, brs), 7.87 (1H, d, J=2.0Hz), 7.63(1H, dd, J=8.4, 2.0Hz), 7.56 (1H, d, J=16.3Hz), 7.16(1H, d, J=8.4Hz), 6.95(1H, d, J=16.3Hz), 4.06(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 3.89(3H, s), 1.26(3H, t, J=6.9Hz), 1.14 (3H, t, J=6.9Hz)

Reference Example 8

(E)-8-(3-Bromo-4-methoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 56)

Substantially the same procedure as in Example 2 was repeated using 400 mg (0.95 mmol) of Compound 55 obtained in Reference Example 7 in place of Compound 1. Then, the resultant crude crystals were recrystallized from dioxane/water to give 332 mg (yield 80%) of Compound 56 as pale yellow needles.

Melting Point: 219.1-223.7°C

Elemental Analysis: $C_{19}H_{21}BrN_4O_3$

Calcd. (%): C, 52.67; H, 4.88; N, 12.93

Found (%): C, 52.79; H, 4.97; N, 12.70

IR (KBr) ν_{max} (cm^{-1}): 1686, 1651, 1541, 1501, 1435

NMR (270MHz; $CDCl_3$) δ (ppm): 7.83(1H, d, J=2.0Hz), 7.69(1H, d, J=15.8Hz), 7.48(1H, dd, J=8.4, 2.0Hz), 6.92(1H, d, J=8.4Hz), 6.78(1H, d, J=15.8Hz), 4.21 (2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.06(3H, s), 3.95(3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 9

(E)-8-(3-Bromo-4-methoxystyryl)theophylline (Compound 57)

Substantially the same procedure as in Example 1 was repeated using 2.00 g (11.8 mmol) of 5,6-diamino-1,3-dimethyluracil and 3.32 g (12.9 mmol) of 3-bromo-4-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dimethylformamide to give 2.00 g (yield 43%) of Compound 57 as a pale yellow powder.

Melting Point: >280°C

Elemental Analysis: $C_{16}H_{15}BrN_4O_3$			
Calcd. (%):	C, 49.12;	H, 3.86;	N, 14.32
Found (%):	C, 49.16;	H, 3.80;	N, 14.06

IR (KBr) ν_{max} (cm^{-1}): 1691, 1644, 1598, 1499, 1257

NMR (270MHz; DMSO-d_6) δ (ppm): 13.41(1H, brs), 7.84 (1H, d, J=2.0Hz), 7.61(1H, dd, J=8.4, 2.0Hz), 7.56 (1H, d, J=16.3Hz), 7.15(1H, d, J=8.4Hz), 6.92(1H, d, J=16.3Hz), 3.89(3H, s), 3.47(3H, s), 3.26(3H, s)

Reference Example 10

(E)-8-(3-Bromo-4-methoxystyryl)caffeine (Compound 58)

Substantially the same procedure as in Example 2 was repeated using 1.00 g (2.56 mmol) of Compound 57 obtained in Reference Example 9 in place of Compound 1. Then, the resultant crude crystals were recrystallized from dioxane to give 877 mg (yield 85%) of Compound 58 as a yellow powder.

Melting Point: 283.3-283.4°C

Elemental Analysis: $C_{17}H_{17}BrN_4O_3$			
Calcd. (%):	C, 50.39;	H, 4.23;	N, 13.83
Found (%):	C, 50.04;	H, 4.00;	N, 13.49

IR (KBr) ν_{max} (cm^{-1}): 1693, 1654, 1500

NMR (270MHz; $CDCl_3$) δ (ppm): 7.82(1H, d, J=2.0Hz), 7.70(1H, d, J=15.8Hz), 7.47(1H, dd, J=8.4, 2.0Hz), 6.92(1H, d, J=8.4Hz), 6.78(1H, d, J=15.8Hz), 4.07 (3H, s), 3.95(3H, s), 3.62(3H, s), 3.42(3H, s)

Reference Example 11

(E)-8-(2-Bromo-4,5-dimethoxystyryl)-1,3-diethylxanthine (Compound 59)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 4.78 g (17.2 mmol) of 2-bromo-4,5-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 3.34 g (yield 49%) of Compound 59 as pale yellow needles.

Melting Point: >285°C

Elemental Analysis: $C_{19}H_{21}BrN_4O_4$			
Calcd. (%):	C, 50.79;	H, 4.71;	N, 12.47
Found (%):	C, 50.49;	H, 4.64;	N, 12.36

IR (KBr) ν_{max} (cm^{-1}): 1693, 1621, 1509, 1260

NMR (270MHz; DMSO-d_6) δ (ppm): 13.65(1H, brs), 7.81 (1H, d, J=16.3Hz), 7.37(1H, s), 7.20(1H, s), 7.06 (1H, d, J=16.3Hz), 4.07(2H, q, J=6.9Hz), 3.95(2H, q, J=6.9Hz), 3.86(3H, s), 3.82(3H, s), 1.27(3H, t, J=6.9Hz), 1.15(3H, t, J=6.9Hz)

Reference Example 12

(E)-8-(2-Bromo-4,5-dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 60)

Substantially the same procedure as in Example 2 was repeated using 1.50 g (3.34 mmol) of Compound 59 obtained in Reference Example 11 in place of Compound 1. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.43 g (yield 92%) of Compound 60 as yellow needles.

Melting Point: 234.2-234.9°C

Elemental Analysis: $C_{20}H_{23}BrN_4O_4$			
Calcd. (%):	C, 51.85;	H, 5.00;	N, 12.09
Found (%):	C, 51.96;	H, 4.95;	N, 11.90

IR (KBr) ν_{max} (cm^{-1}): 1688, 1648, 1504, 1307, 1261

NMR (270MHz; $CDCl_3$) δ (ppm): 8.01(1H, d, J=15.8Hz), 7.11(1H, s), 7.09(1H, s), 6.76(1H, d, J=15.8Hz), 4.22(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.08 (3H, s), 3.95(3H, s), 3.92(3H, s), 1.39(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 13

(E)-8-(4,5-Dimethoxy-2-nitrostyryl)-1,3-diethylxanthine (Compound 61)

Substantially the same procedure as in Example 1 was repeated using 1.50 g (7.57 mmol) of 5,6-diamino-1,3-diethyluracil and 2.11 g (8.33 mmol) of 4,5-dimethoxy-2-nitrocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 1.22 g (yield 39%) of Compound 61 as orange needles.

Melting Point: 283.6-284.2°C

Elemental Analysis: $C_{19}H_{21}N_5O_6$			
Calcd. (%):	C, 54.94;	H, 5.09;	N, 16.86
Found (%):	C, 54.90;	H, 5.07;	N, 16.88

IR (KBr) ν_{max} (cm^{-1}): 1692, 1641, 1520

NMR (270MHz; DMSO-d_6) δ (ppm): 7.99(1H, d, J=16.3Hz), 7.61(1H, s), 7.38(1H, s), 7.15(1H, d, J=16.3Hz), 4.06(2H, q, J=6.9Hz), 3.98(3H, s), 3.95(2H, q, J=6.9Hz), 3.89(3H, s), 1.26(3H, t, J=6.9Hz), 1.15 (3H, t, J=6.9Hz)

Reference Example 14

(E)-8-(4,5-Dimethoxy-2-nitrostyryl)-1,3-diethyl-7-methylxanthine (Compound 62)

Substantially the same procedure as in Example 2 was repeated using 822 mg (1.98 mmol) of Compound 61 obtained in Reference Example 13 in place of Compound 1. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 762 mg (yield 90%) of Compound 62 as orange needles.

Melting Point: 246.3-246.8°C

Elemental Analysis: $C_{20}H_{23}N_5O_6$			
Calcd. (%):	C, 55.94;	H, 5.40;	N, 16.31
Found (%):	C, 55.98;	H, 5.42;	N, 16.43

IR (KBr) ν_{max} (cm^{-1}): 1692, 1657, 1519, 1273

NMR (270MHz; $CDCl_3$) δ (ppm): 8.27(1H, d, J=15.8Hz), 7.66(1H, s), 7.03(1H, s), 6.77(1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.10(3H, s), 4.09(2H, q, J=6.9Hz), 4.05(3H, s), 4.00(3H, s), 1.37(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 15

(E)-1,3-Diethyl-8-(3-methoxy-2-nitrostyryl)xanthine (Compound 63)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.10 g (13.9 mmol) of 3-methoxy-2-nitrocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.28 g (yield 47%) of Compound 63 as orange needles.

Melting Point: >285°C

Elemental Analysis: $C_{18}H_{19}N_5O_5$			
Calcd. (%):	C, 56.10;	H, 4.97;	N, 18.17
Found (%):	C, 56.37;	H, 4.88;	N, 17.85

IR (KBr) ν_{max} (cm^{-1}): 1695, 1640, 1533

NMR (270MHz; DMSO-d_6) δ (ppm): 13.88(1H, brs), 7.60-7.56(2H, m), 7.39(1H, d, J=16.3Hz), 7.32(1H, dd, J=6.9, 3.0Hz), 7.21(1H, d, J=16.3Hz), 4.05(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 3.91(3H, s), 1.25 (3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 16

(E)-1,3-Diethyl-8-(3-methoxy-2-nitrostyryl)-7-methylxanthine (Compound 64)

Substantially the same procedure as in Example 2 was repeated using 688 mg (1.79 mmol) of Compound 63 obtained in Reference Example 15 in place of Compound 1. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 623 mg (yield 87%) of Compound 64 as yellow needles.

Melting Point: 258.4-259.9°C

Elemental Analysis: $C_{19}H_{21}N_5O_5$			
Calcd. (%):	C, 57.14;	H, 5.30;	N, 17.53
Found (%):	C, 57.26;	H, 5.34;	N, 17.26

IR (KBr) ν_{max} (cm^{-1}): 1697, 1546, 1530

NMR (270MHz; $CDCl_3$) δ (ppm): 7.62(1H, d, J=15.3Hz), 7.46(1H, dd, J=8.4, 7.9Hz), 7.30(1H, d, J=7.9Hz), 7.05(1H, d, J=8.4Hz), 6.95(1H, d, J=15.3Hz), 4.19 (2H, q, J=6.9Hz), 4.08(2H, q, J=6.9Hz), 4.05(3H, s), 3.94(3H, s), 1.36(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 17

(E)-1,3-Diethyl-8-(3-fluorostyryl)xanthine (Compound 65)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.77 g (16.7 mmol) of 3-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.96 g (yield 40%) of Compound 65 as a pale yellow powder.

Melting Point: >270°C

Elemental Analysis: $C_{17}H_{17}FN_4O_2$			
Calcd. (%):	C, 62.19;	H, 5.22;	N, 17.06
Found (%):	C, 61.90;	H, 5.21;	N, 17.15

IR (KBr) ν_{max} (cm^{-1}): 1692, 1622, 1501

NMR (270MHz; CF_3COOD) δ (ppm): 11.6(1H, brs), 8.05(1H, d, J=16.5Hz), 7.56-7.46(2H, m), 7.38(1H, d, J=9.2Hz), 7.29-7.22(1H, m), 7.19(1H, d, J=16.5Hz), 4.43-4.03(4H, m), 1.52(3H, t, J=7.3Hz), 1.41(3H, t, J=6.9Hz)

Reference Example 18

(E)-1,3-Diethyl-8-(3-fluorostyryl)-7-methylxanthine (Compound 66)

Substantially the same procedure as in Example 2 was repeated using 1.80 g (5.49 mmol) of Compound 65 obtained in Reference Example 17 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.04 g (yield 55%) of Compound 66 as white needles.

Melting Point: 178.2-179.4°C

Elemental Analysis: $C_{18}H_{19}FN_4O_2 \cdot 0.25H_2O$			
Calcd. (%):	C, 62.33;	H, 5.67;	N, 16.15
Found (%):	C, 62.19;	H, 5.63;	N, 16.26

IR (KBr) ν_{max} (cm^{-1}): 1694, 1650

NMR (270MHz; DMSO-d_6) δ (ppm): 7.75(1H, dd, J=10.1, 2.0Hz), 7.66(1H, d, J=15.8Hz), 7.63-7.60(1H, m), 7.50-7.42(1H, m), 7.44(1H, d, J=15.8Hz), 7.19(1H, dt, J=2.0, 8.3Hz), 4.10-4.05(2H, m), 4.05(3H, s), 3.92(2H, q, J=7.0Hz), 1.26(3H, t, J=7.1Hz), 1.13 (3H, t, J=7.0Hz)

Reference Example 19

(E)-8-(3,5-Dimethoxystyryl)-1,3-diethylxanthine (Compound 67)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.48 g (16.7 mmol) of 3,5-dimethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/water to give 2.74 g (yield 49%) of Compound 67 as a white powder.

Melting Point: >270°C

Elemental Analysis: $C_{19}H_{22}N_4O_4 \cdot 0.5H_2O$			
Calcd. (%):	C, 60.15;	H, 6.11;	N, 14.77
Found (%):	C, 60.41;	H, 6.15;	N, 15.02

IR (KBr) ν_{max} (cm^{-1}): 1686, 1638, 1587

NMR (270MHz; DMSO-d_6) δ (ppm): 7.57(1H, d, J=16.5Hz), 7.07(1H, d, J=16.5Hz), 6.79(2H, d, J=2.0Hz), 6.50 (1H, t, J=2.0Hz), 4.06(2H, q, J=7.0Hz), 3.94(2H, q, J=6.9Hz), 3.79(6H,s), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 20

(E)-8-(3,5-Dimethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 68)

Substantially the same procedure as in Example 2 was repeated using 3.00 g (8.11 mmol) of Compound 67 obtained in Reference Example 19 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 2.28 g (yield 73%) of Compound 68 as yellow needles.

Melting Point: 184.2-185.3°C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.49;	H, 6.29;	N, 14.57
Found (%):	C, 62.66;	H, 6.48;	N, 14.65

IR (KBr) ν_{max} (cm^{-1}): 1690, 1659, 1595

NMR (270MHz; DMSO-d_6) δ (ppm): 7.60(1H, d, J=15.7Hz), 7.35(1H, d, J=15.7Hz), 6.98(2H, d, J=2.2Hz), 6.51 (1H, t, J=2.2Hz), 4.11-4.01(2H, m), 4.05(3H, s), 3.92(2H, q, J=7.0Hz), 3.80(6H, s), 1.26(3H, t, J=7.1Hz), 1.13(3H, t, J=7.0Hz)

Reference Example 21

(E)-8-(3-Chlorostyryl)-1,3-diethylxanthine (Compound 69)

Substantially the same procedure as in Example 1 was repeated using 3.50 g (17.7 mmol) of 5,6-diamino-1,3-diethyluracil and 3.55 g (19.4 mmol) of 3-chlorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.57 g (yield 42%) of Compound 69 as white plates.

Melting Point: >280°C

Elemental Analysis: $C_{17}H_{17}ClN_4O_2$			
Calcd. (%):	C, 59.22;	H, 4.97;	N, 16.25
Found (%):	C, 59.12;	H, 5.01;	N, 16.30

IR (KBr) ν_{max} (cm^{-1}): 1689, 1640, 1490

NMR (270MHz; CF_3COOD) δ (ppm): 8.35(1H, d, J=16.4Hz), 8.01(1H, s), 7.52-7.36(3H, m), 7.14(1H, d, J=16.4Hz), 4.37-4.23(4H, m), 1.45(3H, t, J=6.8Hz), 1.34(3H, t, J=6.9Hz)

Reference Example 22

(E)-8-(3-Chlorostyryl)-1,3-diethyl-7-methylxanthine (Compound 70)

Substantially the same procedure as in Example 2 was repeated using 3.00 g (8.72 mmol) of Compound 69 obtained in Reference Example 21 in place of Compound 1. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.41 g (yield 45%) of Compound 70 as a pale yellow powder.

Melting Point: 134.0-134.4°C

Elemental Analysis: $C_{18}H_{19}ClN_4O_2 \cdot H_2O$			
Calcd. (%):	C, 57.37;	H, 5.62;	N, 14.87
Found (%):	C, 57.67;	H, 5.51;	N, 14.92

IR (KBr) ν_{max} (cm^{-1}): 1688, 1656, 1545

NMR (270MHz; DMSO-d_6) δ (ppm): 7.98(1H, s), 7.72(1H, t, J=2.0Hz), 7.63(1H, d, J=15.8Hz), 7.49-7.39(3H, m), 4.11-4.03(2H, m), 4.05(3H, s), 3.92(2H, q, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 23

(E)-1,3-Diethyl-8-(α-methylstyryl)xanthine (Compound 71)

Substantially the same procedure as in Example 1 was repeated using 2.00 g (10.1 mmol) of 5,6-diamino-

1,3-diethyluracil and 1.80 g (11.1 mmol) of α-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from ethanol/water to give 1.63 g (yield 50%) of Compound 71 as white needles.

Melting Point: 250.8-252.0°C

Elemental Analysis: $C_{18}H_{20}N_4O_2$			
Calcd. (%):	C, 66.65;	H, 6.21;	N, 17.27
Found (%):	C, 66.62;	H, 6.30;	N, 17.31

IR (KBr) ν_{max} (cm^{-1}): 1696, 1657, 1493

NMR (270MHz; DMSO-d_6) δ (ppm): 13.44(1H, brs), 7.61 (1H, d, J=1.3Hz), 7.49-7.30(6H, m), 4.07(2H, q, J=7.0Hz), 3.95(2H, q, J=6.9Hz), 2.31(3H, d, J=1.3Hz), 1.26(3H, t, J=7.0Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 24

(E)-1,3-Diethyl-7-methyl-8-(α-methylstyryl)xanthine (Compound 72)

Substantially the same procedure as in Example 2 was repeated using 1.00 g (3.09 mmol) of Compound 71 obtained in Reference Example 23 in place of Compound 1. Then, the resultant crude crystals were recrystallized from ethanol/2-propanol to give 800 mg (yield 77%) of Compound 72 as white needles.

Melting Point: 137.2-139.3°C

Elemental Analysis: $C_{19}H_{22}N_4O_2$			
Calcd. (%):	C, 67.44;	H, 6.55;	N, 16.56
Found (%):	C, 67.01;	H, 6.73;	N, 16.62

IR (KBr) ν_{max} (cm^{-1}): 1699, 1654, 1537

NMR (270MHz; DMSO-d_6) δ (ppm): 7.52-7.32(5H, m), 7.00 (1H, d, J=1.3Hz), 4.04(2H, q, J=7.2Hz), 4.00(3H, s), 3.94(2H, q, J=6.9Hz), 2.29(3H, d, J=1.3Hz), 1.24(3H, t, J=7.2Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 25

(E)-1,3-Diethyl-8-(4-trifluoromethylstyryl)xanthine (Compound 73)

Substantially the same procedure as in Example 1 was repeated using 2.20 g (11.2 mmol) of 5,6-diamino-1,3-diethyluracil and 2.66 g (12.3 mmol) of 4-trifluoromethylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.09 g (yield 49%) of Compound 73 as a white powder.

Melting Point: >280°C

Elemental Analysis: $C_{18}H_{17}F_3N_4O_2$			
Calcd. (%):	C, 57.14;	H, 4.53;	N, 14.81
Found (%):	C, 57.25;	H, 4.51;	N, 14.82

IR (KBr) ν_{max} (cm^{-1}): 1696, 1654, 1637, 1324

NMR (270MHz; DMSO-d_6) δ (ppm): 7.86(2H, d, J=8.1Hz), 7.76(2H, d, J=8.1Hz), 7.70(1H, d, J=16.5Hz), 7.20 (1H, d, J=16.5Hz), 4.07(2H, q, J=7.1Hz), 3.94(2H, q, J=7.0Hz), 1.26(3H, t, J=7.1Hz), 1.14(3H, t, J=7.0Hz)

Reference Example 26

(E)-1,3-Diethyl-7-methyl-8-(4-trifluoromethylstyryl)xanthine (Compound 74)

Substantially the sam procedure as in Example 2 was r p ated using 1.30 g (3.44 mmol) of Compound 73 obtain d in Reference Example 25 in place of Compound 1. Then, th resultant crude crystals were recrystalliz d from toluene/cyclohexane to give 990 mg (yield 73%) of Compound 74 as yellow needles.

M lting Point: 207.8-209.0°C

Elemental Analysis: $C_{19}H_{19}F_3N_4O_2$			
Calcd. (%):	C, 58.16;	H, 4.88;	N, 14.28
Found (%):	C, 58.22;	H, 4.84;	N, 14.32

IR (KBr) ν_{max} (cm^{-1}): 1700, 1667, 1325

NMR (270MHz; DMSO-d_6) δ (ppm): 8.03(2H, d, J=8.3Hz), 7.76(2H, d, J=8.3Hz), 7.73(1H, d, J=15.8Hz), 7.53 (1H, d, J=15.8Hz), 4.11-4.03(2H, m), 4.09(3H, s), 3.92(2H, q, J=7.0Hz), 1.27(3H, t, J=6.9Hz), 1.13(3H, t, J=7.0Hz)

Reference Example 27

(E)-1,3-Diethyl-8-(α-fluorostyryl)xanthine (Compound 75)

Substantially the same procedure as in Example 1 was repeated using 1.08 g (5.47 mmol) of 5,6-diamino-1,3-diethyluracil and 1.00 g (6.02 mmol) of α-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.04 g (yield 58%) of Compound 75 as white plates.

Melting Point: >280°C

Elemental Analysis: $C_{17}H_{17}FN_4O_2$			
Calcd. (%):	C, 62.19;	H, 5.22;	N, 17.06
Found (%):	C, 62.28;	H, 5.22;	N, 17.07

IR (KBr) ν_{max} (cm^{-1}): 1695, 1644, 1506

NMR (270MHz; DMSO-d_6) δ (ppm): 7.68(2H, d, J=6.9Hz), 7.47-7.35(3H, m), 6.93(1H, d, J=36.3Hz), 4.06(2H, q, J=6.9Hz), 3.94(2H, q, J=7.0Hz), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=7.0Hz)

Reference Example 28

(E)-1,3-Diethyl-8-(α-fluorostyryl)-7-methylxanthine (Compound 76)

Substantially the same procedure as in Example 2 was repeated using 800 mg (2.44 mmol) of Compound 75 obtained in Reference Example 27 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 550 mg (yield 66%) of Compound 76 as a white powder.

Melting Point: 153.5-155.5°C

Elemental Analysis: $C_{18}H_{19}FN_4O_2$			
Calcd. (%):	C, 63.15;	H, 5.59;	N, 16.36
Found (%):	C, 63.25;	H, 5.66;	N, 16.44

IR (KBr) ν_{max} (cm^{-1}): 1696, 1662, 1539

NMR (270MHz; $CDCl_3$) δ (ppm): 7.68-7.65(2H, m) , 7.47-7.31(3H, m), 6.89(1H, d, J=39.3Hz), 4.13-4.05(2H, m), 4.21(3H, s), 4.09(2H, q, J=7.1Hz), 1.37(3H, t, J=7.1Hz), 1.27(3H, t, J=7.1Hz)

Reference Example 29

(E)-8-(4-Bromostyryl)-1,3-diethylxanthine (Compound 77)

Substantially the same procedure as in Example 1 was repeated using 2.20 g (11.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.78 g (12.2 mmol) of 4-bromocinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 930 mg (yield 22%) of Compound 77 as yellow columns.

Melting Point: >270°C

Elemental Analysis: $C_{17}H_{17}BrN_4O_2$			
Calcd. (%):	C, 52.46;	H, 4.40;	N, 14.39
Found (%):	C, 52.41;	H, 4.28;	N, 14.43

IR (KBr) ν_{max} (cm^{-1}): 1686, 1619, 1496

NMR (270MHz; DMSO-d_6) δ (ppm): 7.63-7.18(4H, m), 7.60 (1H, d, J=16.2Hz), 7.07(1H, d, J=16.2Hz), 4.06(2H, q, J=6.9Hz), 3.94(2H, q, J=6.8Hz), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.8Hz)

Reference Example 30

(E)-8-(4-Bromostyryl)-1,3-diethyl-7-methylxanthine (Compound 78)

Substantially the same procedure as in Example 2 was repeated using 1.80 g (4.63 mmol) of Compound 77 obtained in Reference Example 29 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/ethanol to give 660 mg (yield 35%) of Compound 78 as pale yellow needles.

Melting Point: 198.5-198.9°C

Elemental Analysis: $C_{18}H_{19}BrN_4O_2 \cdot 0.25H_2O$

Calcd. (%): C, 53.02; H, 4.82; N, 13.74

Found (%): C, 53.09; H, 4.62; N, 13.79

IR (KBr) ν_{max} (cm^{-1}): 1691, 1662, 1543

NMR (270MHz; DMSO-d_6) δ (ppm): 7.78(2H, d, J=7.6Hz), 7.67-7.61(3H, m), 7.41(1H, d, J=16.2Hz), 4.11-4.04 (2H, m), 4.04(3H, s), 3.92(2H, q, J=6.7Hz), 1.26 (3H, t, J=6.8Hz), 1.13(3H, t, J=6.7Hz)

Reference Example 31

(E)-1,3-Diethyl-8-(3-trifluoromethoxystyryl)xanthine (Compound 79)

Substantially the same procedure as in Example 1 was repeated using 1.00 g (5.05 mmol) of 5,6-diamino-1,3-diethyluracil and 1.29 g (5.56 mmol) of 3-trifluoromethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.19 g (yield 60%) of Compound 79 as white needles.

Melting Point: 266.4-267.3°C

Elemental Analysis: $C_{18}H_{17}F_3N_4O_3$			
Calcd. (%):	C, 54.83;	H, 4.34;	N, 14.21
Found (%):	C, 54.79;	H, 4.22;	N, 14.20

IR (KBr) ν_{max} (cm^{-1}): 1697, 1658, 1500, 1262

NMR (270MHz; DMSO-d_6) δ (ppm): 13.57(1H, brs), 7.67 (1H, d, J=16.5Hz), 7.66(1H, d, J=7.9Hz), 7.63(1H, s), 7.55(1H, t, J=7.9Hz), 7.34(1H, d, J=7.9Hz), 7.14(1H, d, J=16.5Hz), 4.07(2H, q, J=6.9Hz), 3.94 (2H, q, J=6.9Hz), 1.27(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 32

(E)-1,3-Diethyl-7-methyl-8-(3-trifluoromethoxystyryl)xanthine (Compound 80)

Substantially the same procedure as in Example 2 was repeated using 700 mg (1.78 mmol) of Compound 79 obtained in Reference Example 31 in place of Compound 1. Then, the resultant crude crystals were recrystallized from ethyl ac tate to give 329 mg (yield 45%) of Compound 80 as white n edles.

Melting Point: 178.7-179.3°C

El mental Analysis: $C_{19}H_{19}F_3N_4O_3$			
Calcd. (%):	C, 55.88;	H, 4.69;	N, 13.72
Found (%):	C, 56.27;	H, 4.68;	N, 13.67

IR (KBr) ν_{max} (cm^{-1}): 1694, 1660, 1265, 1213

NMR (270MHz; $CDCl_3$) δ (ppm): 7.77(1H, d, J=15.8Hz), 7.53-7.20(4H, m), 6.93(1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.08(3H, s), 1.38(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 33

(E)-1,3-Diethyl-8-(4-methoxymethoxystyryl)xanthine (Compound 81)

Substantially the same procedure as in Example 1 was repeated using 4.00 g (20.2 mmol) of 5,6-diamino-1,3-diethyluracil and 4.62 g (22.2 mmol) of 4-methoxymethoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 4.80 g (yield 64%) of Compound 81 as pale yellow needles.

Melting Point: 270.2-271.4°C

Elemental Analysis: $C_{19}H_{22}N_4O_4$			
Calcd. (%):	C, 61.61;	H, 5.98;	N, 15.13
Found (%):	C, 61.97;	H, 5.98;	N, 15.05

IR (KBr) ν_{max} (cm^{-1}): 1695, 1641, 1510, 1238

NMR (270MHz; DMSO-d_6) δ (ppm): 13.40(1H, brs), 7.60 (1H, d, J=16.5Hz), 7.57(2H, d, J=8.6Hz), 7.06(2H, d, J=8.6Hz), 6.90(1H, d, J=16.5Hz), 5.23(2H, s), 4.07(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 3.39 (3H, s), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 34

(E)-1,3-Diethyl-8-(4-methoxymethoxystyryl)-7-methylxanthine (Compound 82)

Substantially the same procedure as in Example 2 was repeated using 3.50 g (9.45 mmol) of Compound 81 obtained in Reference Example 33 in place of Compound 1. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 3.39 g (yield 93%) of Compound 82 as pale yellow plates.

Melting Point: 163.9-164.7°C

Elemental Analysis: $C_{20}H_{24}N_4O_4$			
Calcd. (%):	C, 62.49;	H, 6.29;	N, 14.57
Found (%):	C, 62.21;	H, 6.27;	N, 14.58

IR (KBr) ν_{max} (cm^{-1}): 1688, 1651, 1510, 1238

NMR (270MHz; $CDCl_3$) δ (ppm): 7.75(1H, d, J=15.8Hz), 7.53(2H, d, J=8.6Hz), 7.07(2H, d, J=8.6Hz), 6.79 (1H, d, J=15.8Hz), 5.21(2H, s), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.05(3H, s), 3.50 (3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 35

(E)-1,3-Diethyl-8-(4-fluorostyryl)xanthine (Compound 83)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.31 g (13.9 mmol) of 4-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 2.00 g (yield 51%) of Compound 83 as colorless columns.

Melting Point: >270°C

Elemental Analysis: $C_{17}H_{17}FN_4O_2$			
Calcd. (%):	C, 62.19;	H, 5.22;	N, 17.06
Found (%):	C, 62.02;	H, 5.12;	N, 17.02

IR (KBr) ν_{max} (cm^{-1}): 1689, 1560, 1508

NMR (270MHz; DMSO-d_6) δ (ppm): 8.06(1H, d, J=16.3Hz), 7.72(2H, dd, J=8.6, 5.2Hz), 7.21(2H, t, J=8.6Hz), 7.10(1H, d, J=16.3Hz), 4.43-4.30(4H, m), 1.53(3H, t, J=7.2Hz), 1.41(3H, t, J=7.2Hz)

Reference Example 36

(E)-1,3-Diethyl-8-(4-fluorostyryl)-7-methylxanthine (Compound 84)

Substantially the same procedure as in Example 2 was repeated using 1.80 g (5.18 mmol) of Compound 83 obtained in Reference Example 35 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 510 mg (yield 29%) of Compound 84 as white needles.

Melting Point: 182.0-182.5°C

Elemental Analysis: $C_{18}H_{19}FN_4O_2$			
Calcd. (%):	C, 63.15;	H, 5.59;	N, 16.36
Found (%):	C, 63.18;	H, 5.61;	N, 16.40

IR (KBr) ν_{max} (cm^{-1}): 1687, 1654, 1514

NMR (270MHz; DMSO-d_6) δ (ppm): 7.88(2H, dd, J=8.1, 5.8Hz), 7.67(1H, d, J=15.8Hz), 7.41-7.24(3H, m), 4.11-4.03(2H, m), 4.03(3H, s), 3.92(2H, q, J=6.8Hz), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=6.8Hz)

Reference Example 37

(E)-8-[3,5-Bis(trifluoromethyl)styryl]-1,3-diethylxanthine (Compound 85)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 4.73 g (16.7 mmol) of 3,5-bis(trifluoromethyl)cinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 4.09 g (yield 61%) of Compound 85 as pale yellow needles.

Melting Point: >280°C

Elemental Analysis: $C_{19}H_{16}F_6N_4O_2$			
Calcd. (%):	C, 51.13;	H, 3.61;	N, 12.55
Found (%):	C, 50.96;	H, 3.40;	N, 12.52

IR (KBr) ν_{max} (cm^{-1}): 1694, 1649, 1495, 1287

NMR (270MHz; DMSO-d_6) δ (ppm): 13.75(1H, brs), 8.35 (2H, s), 8.05(1H, s), 7.80(1H, d, J=16.5Hz), 7.40 (1H, d, J=16.5Hz), 4.08(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 1.27(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 38

(E)-8-[3,5-Bis(trifluoromethyl)styryl]-1,3-diethyl-7-methylxanthine (Compound 86)

Substantially the same procedure as in Example 2 was repeated using 2.00 g (4.68 mmol) of Compound 85 obtained in Reference Example 37 in place of Compound 1. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.43 g (yield 69%) of Compound 86 as pale green needles.

Melting Point: 204.9-205.1°C

MS-EI m/e: 460(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1699, 1653, 1546, 1282

NMR (270MHz; $CDCl_3$) δ (ppm): 8.55(2H, s), 8.01(1H, s), 7.85(1H, d, J=15.8Hz), 7.72(1H, d, J=15.8Hz), 4.09 (3H, s), 4.08(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 1.28(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 39

(E)-8-(3,5-Difluorostyryl)-1,3-diethylxanthine (Compound 87)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.06 g (16.6 mmol) of 3,5-difluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.30 g (yield 63%) of Compound 87 as pale yellow plates.

Melting Point: >280°C

Elemental Analysis: $C_{17}H_{16}F_2N_4O_2$			
Calcd. (%):	C, 58.96;	H, 4.65;	N, 16.18
Found (%):	C, 58.82;	H, 4.65;	N, 16.07

IR (KBr) ν_{max} (cm^{-1}): 1686, 1634, 1589, 1489

NMR (270MHz; DMSO-d_6) δ (ppm): 13.66(1H, brs), 7.60 (1H, d, J=16.5Hz), 7.36(2H, dd, J=8.6, 2.0Hz), 7.20(1H, dt, J=9.2, 2.0Hz), 7.16(1H, d, J=16.5Hz), 4.07(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 1.26 (3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 40

(E)-8-(3,5-Difluorostyryl)-1,3-diethyl-7-methylxanthine (Compound 88)

Substantially the same procedure as in Example 2 was repeated using 2.00 g (5.78 mmol) of Compound 87 obtained in Reference Example 39 in place of Compound 1. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.80 g (yield 87%) of Compound 88 as pale yellow needles.

Melting Point: 177.0-178.6°C

MS-EI m/e: 360(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1683, 1619, 1593, 1543

NMR (270MHz; $CDCl_3$) δ (ppm): 7.70(1H, d, J=15.5Hz), 7.09(2H, dd, J=8.3, 2.0Hz), 6.91(1H, d, J=15.5Hz), 6.81(1H, dt, J=8.6, 2.0Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.08(3H, s), 1.38(3H, t, J=6.9Hz), 1.27(3H, t, J=6.9Hz)

Reference Example 41

(E)-1,3-Diethyl-8-(3-nitrostyryl)xanthine (Compound 89)

Substantially the same procedure as in Example 1 was repeated using 2.5 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.68 g (13.9 mmol) of 3-nitrocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 2.01 g (yield 30%) of Compound 89 as a yellow powder.

Melting Point: >270°C

Elemental Analysis: $C_{17}H_{17}N_5O_4 \cdot 0.25C_4H_8O_2$			
Calcd. (%):	C, 57.29;	H, 5.07;	N, 18.56
Found (%):	C, 57.38;	H, 5.06;	N, 18.63

IR (KBr) ν_{max} (cm^{-1}): 1688, 1640, 1530

NMR (270MHz; DMSO-d_6) δ (ppm): 8.42(1H, d, J=1.7Hz), 8.18(1H, dd, J=8.3, 1.7Hz), 8.12(1H, d, J=7.9Hz), 7.75(1H, d, J=16.5Hz), 7.71(1H, t, J=7.9Hz), 7.24 (1H, d, J=16.5Hz), 4.08(2H, q, J=7.0Hz), 3.94(2H, q, J=7.0Hz), 1.27(3H, t, J=7.0Hz), 1.14(3H, t, J=7.0Hz)

Reference Example 42

(E)-1,3-Diethyl-7-methyl-8-(3-nitrostyryl)xanthine (Compound 90)

Substantially the same procedure as in Example 2 was repeated using 700 mg (1.97 mmol) of Compound 89 obtained in Reference Example 41 in place of Compound 1. Then, the resultant crude crystals were recrystallized from acetonitrile to give 340 mg (yield 47%) of Compound 90 as a yellow powder.

Melting Point: 250.5-251.7°C

Elemental Analysis: $C_{18}H_{19}N_5O_4$			
Calcd. (%):	C, 58.53;	H, 5.18;	N, 18.96
Found (%):	C, 58.47;	H, 5.13;	N, 18.89

IR (KBr) ν_{max} (cm^{-1}): 1699, 1666, 1524

NMR (270MHz; DMSO-d_6) δ (ppm): 8.72(1H, s), 8.25(1H, d, J=7.9Hz), 8.19(1H, d, J=7.4Hz), 7.79(1H, d, J=15.8Hz), 7.72(1H, t, J=7.9Hz), 7.63(1H, d, J=15.8Hz), 4.12-4.05(2H, m), 4.08(3H, s), 3.93(2H, q, J=7.2Hz), 1.27(3H, t, J=7.2Hz), 1.13(3H, t, J=7.2Hz)

Reference Example 43

(E)-8-(3-Bromostyryl)-1,3-diethylxanthine (Compound 91)

Substantially the same procedure as in Example 1 was repeated using 2.0 g (10.1 mmol) of 5,6-diamino-1,3-diethyluracil and 2.52 g (11.1 mmol) of 3-bromocinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 2.01 g (yield 37%) of Compound 91 as pale green plates.

Melting Point: >270°C

Elemental Analysis: $C_{17}H_{17}BrN_4O_2$			
Calcd. (%):	C, 52.46;	H, 4.40;	N, 14.39
Found (%):	C, 52.54;	H, 4.44;	N, 14.37

IR (KBr) ν_{max} (cm^{-1}): 1683, 1636, 1492

NMR (270MHz; CF_3COOD) δ (ppm): 7.99(1H, d, J=16.6Hz), 7.84(1H, s), 7.70(1H, d, J=7.9Hz), 7.62(1H, d, J=7.9Hz), 7.40(1H, t, J=7.9Hz), 7.19(1H, d, J=16.6Hz), 4.40-4.30(4H, m), 1.53(3H, t, J=7.2Hz), 1.41(3H, t, J=7.2Hz)

Reference Example 44

(E)-8-(3-Bromostyryl)-1,3-diethyl-7-methylxanthine (Compound 92)

Substantially the same procedure as in Example 2 was repeated using 2.5 g (6.43 mmol) of Compound 91 obtained in Reference Example 43 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 600 mg (yield 69%) of Compound 92 as a yellow powder.

Melting Point: 187.3-188.2°C

Elemental Analysis: $C_{18}H_{19}BrN_4O_2$			
Calcd. (%):	C, 53.61;	H, 4.75;	N, 13.89
Found (%):	C, 53.83;	H, 4.63;	N, 13.70

IR (KBr) ν_{max} (cm^{-1}): 1694, 1654

NMR (270MHz; DMSO-d_6) δ (ppm): 8.13(1H, s), 7.76(1H, d, J=7.6Hz), 7.63(1H, d, J=15.8Hz), 7.54(1H, d, J=8.9Hz), 7.46(1H, d, J=15.8Hz), 7.37(1H, t, J=8.2Hz), 4.11-4.03(2H, m), 4.05(3H, s), 3.92(2H, q, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 45

(E)-1,3-Diethyl-8-(3-trifluoromethylstyryl)xanthine (Compound 93)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.0 g (13.9 mmol) of 3-trifluoromethylcinnamic acid. Then, the resultant crude crystals were recrystallized from acetonitrile/water to give 2.07 g (yield 44%) of Compound 93 as whit needles.

Melting Point: >270°C

Elemental Analysis: $C_{18}H_{17}F_3N_4O_2$			
Calcd. (%):	C, 57.14;	H, 4.53;	N, 14.81
Found (%):	C, 57.15;	H, 4.47;	N, 14.65

IR (KBr) ν_{max} (cm^{-1}): 1691, 1641, 1495, 1334

NMR (270MHz; DMSO-d_6) δ (ppm): 13.65(1H, brs), 7.99-7.95(2H, m), 7.76-7.63(3H, m), 7.21(1H, d, J=16.1Hz), 4.07(2H, q, J=6.9Hz), 3.94 (2H, q, J=6.7Hz), 1.27(3H, t, J=6.9Hz), 1.14(3H, t, J=6.7Hz)

Reference Example 46

(E)-1,3-Diethyl-7-methyl-8-(3-trifluoromethylstyryl)xanthine (Compound 94)

Substantially the same procedure as in Example 2 was repeated using 1.70 g (4.50 mmol) of Compound 93 obtained in Reference Example 45 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to give 1.14 g (yield 65%) of Compound 94 as a pale yellow powder.

Melting Point: 214.8-215.3°C

Elemental Analysis: $C_{19}H_{19}F_3N_4O_2$			
Calcd. (%):	C, 58.16;	H, 4.88;	N, 14.28
Found (%):	C, 58.13;	H, 4.90;	N, 14.22

IR (KBr) ν_{max} (cm^{-1}): 1697, 1664

NMR (270MHz; DMSO-d_6) δ (ppm): 8.26(1H, s), 8.09(1H, d, J=7.4Hz), 7.75(1H, d, J=15.8Hz), 7.69-7.62(2H, m), 7.56(1H, d, J=15.8Hz), 4.12-4.00(2H, m), 4.07 (3H, s), 3.92(2H, q, J=6.9Hz), 1.27(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 47

(E)-1,3-Diethyl-8-(2-fluorostyryl)xanthine (Compound 97)

Substantially the same procedure as in Example 1 was repeated using 2.70 g (13.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.49 g (15.0 mmol) of 2-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.81 g (yield 41%) of Compound 97 as a white powder.

Melting Point: >270°C

Elemental Analysis: $C_{17}H_{17}FN_4O_2$			
Calcd. (%):	C, 62.19;	H, 5.22;	N, 17.06
Found (%):	C, 62.31;	H, 5.23;	N, 17.09

IR (KBr) ν_{max} (cm^{-1}): 1687, 1650, 1557, 1498, 1451

NMR (270MHz; DMSO-d_6) δ (ppm): 7.81(1H, t, J=7.9Hz), 7.72(1H, d, J=16.3Hz), 7.42-7.25(3H, m), 7.15 (1H, d, J=16.3Hz), 4.07(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 48

(E)-1,3-Diethyl-8-(2-fluorostyryl)-7-methylxanthine (Compound 98)

Substantially the same procedure as in Example 2 was repeated using 1.30 g (3.96 mmol) of Compound 97 obtained in Reference Example 47 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/cyclohexane to giv 440 mg (yield 32%) of Compound 98 as white needles.

Melting Point: 184.1-184.6°C

Elemental Analysis: $C_{18}H_{19}FN_4O_2$			
Calcd. (%):	C, 63.15;	H, 5.59;	N, 16.36
Found (%):	C, 63.01;	H, 5.61;	N, 16.27

IR (KBr) ν_{max} (cm^{-1}): 1697, 1668, 1541

NMR (270MHz; DMSO-d_6) δ (ppm): 8.04(1H, t, J=8.4Hz), 7.77(1H, d, J=15.8Hz), 7.47-7.43(1H, m), 7.45(1H, d, J=15.8Hz), 7.35-7.27(2H, m), 4.11-4.04(2H, m), 4.04(3H, s), 3.92(2H, q, J=7.0Hz), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=7.0Hz)

Reference Example 49

(E)-8-[4-(N,N-Dimethylamino)styryl]-1,3-diethylxanthine (Compound 99)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 3.30 g (17.3 mmol) of 4-(N,N-dimethylamino)cinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 2.78 g (yield 52%) of Compound 99 as yellow needles.

Melting Point: >300°C

Elemental Analysis: $C_{19}H_{23}N_5O_2$			
Calcd. (%):	C, 64.57;	H, 6.56;	N, 19.82
Found (%):	C, 64.78;	H, 6.73;	N, 19.94

IR (KBr) ν_{max} (cm^{-1}): 1691, 1650, 1606, 1530

NMR (270MHz; DMSO-d_6) δ (ppm): 13.20(1H, brs), 7.54 (1H, d, J=16.2Hz), 7.44(2H, d, J=8.6Hz), 6.75(1H, d, J=16.2Hz), 6.74(2H, d, J=8.6Hz), 4.06(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 2.97(6H, s), 1.26 (3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 50

(E)-1,3-Diethyl-8-(4-phenylstyryl)xanthine (Compound 100)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 3.12 g (13.9 mmol) of 4-phenylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.90 g (yield 39%) of Compound 100 as yellow flocculent precipitates.

Melting Point: >270°C

Elemental Analysis: $C_{23}H_{22}N_4O_2 \cdot 0.25H_2O$			
Calcd. (%):	C, 70.66;	H, 5.80;	N, 14.33
Found (%):	C, 70.90;	H, 5.75;	N, 14.32

IR (KBr) ν_{max} (cm^{-1}): 1689, 1639, 1492

NMR (270MHz; DMSO-d_6) δ (ppm): 7.80-7.65(7H, m), 7.49 (2H, t, J=7.3Hz), 7.39(1H, t, J=7.3Hz), 7.10(1H, d, J=16.3Hz), 4.07(2H, q, J=7.1Hz), 3.94(2H, q, J=6.8Hz), 1.27(3H, t, J=7.1Hz), 1.14(3H, t, J=6.8Hz)

Reference Example 51

(E)-1,3-Diethyl-7-methyl-8-(4-phenylstyryl)xanthine (Compound 101)

Compound 100 (1.50 g, 3.89 mmol) obtained in Reference Example 50 was suspended in a mixed solvent of 13 ml of water, 3.9 ml of a 2N aqueous solution of sodium hydroxide, and 7 ml of methanol. To the suspension was dropwise added 0.55 ml (5.83 mmol) of dimethyl sulfate, and the resultant mixture was stirred at 60°C for 4 hours. Water (10 ml) was added thereto, and th deposited crystals were collected by filtration and dried. The obtained crude crystals were purified by silica gel column chromatography, followed by recrystallization from ethyl acetate to give 480 mg (yield 28%) of Compound 101 as yellow columns.

Melting Point: 200.5-201.3°C

Elemental Analysis: $C_{24}H_{24}N_4O_2 \cdot 0.5CH_3CO_2C_2H_5$			
Calcd. (%):	C, 70.25;	H, 6.35;	N, 12.72
Found (%):	C, 70.36;	H, 6.47;	N, 12.60

IR (KBr) ν_{max} (cm^{-1}): 1685, 1649, 1541

NMR (270MHz; DMSO-d_6) δ (ppm): 7.95(1H, d, J=14.8Hz), 7.76-7.69(6H, m), 7.52-7.45(3H, m), 7.39(1H, t, J=6.4Hz), 4.12-3.99(2H, m), 4.06(3H, s), 3.92(2H, q, J=6.9Hz), 1.27(3H, t, J=6.9Hz), 1.14(3H, t, J=7.0Hz)

Reference Example 52

(E)-1,3-Diethyl-8-(3-fluoro-4-methoxystyryl)xanthine (Compound 102)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.72 g (13.9 mmol) of 3-fluoro-4-methoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 1.97 g (yield 44%) of Compound 102 as pale yellow flocculent precipitates.

Melting Point: >270°C

Elemental Analysis: $C_{18}H_{19}FN_4O_3$			
Calcd. (%):	C, 60.33;	H, 5.34;	N, 15.63
Found (%):	C, 59.99;	H, 5.34;	N, 15.57

IR (KBr) ν_{max} (cm^{-1}): 1694, 1644, 1520, 1491

NMR (270MHz; DMSO-d_6) δ (ppm): 7.61-7.54(2H, m), 7.40 (1H, d, J=8.8Hz), 7.21(1H, t, J=8.8Hz), 6.93(1H, d, J=16.3Hz), 4.06(2H, q, J=7.1Hz), 3.97-3.88(2H, m), 3.88(3H, s), 1.25(3H, t, J=7.2Hz), 1.14(3H, t, J=7.1Hz)

Reference Example 53

(E)-1,3-Diethyl-8-(3-fluoro-4-methoxystyryl)-7-methylxanthine (Compound 103)

Substantially the same procedure as in Example 2 was repeated using 1.50 g (4.19 mmol) of Compound 102 obtained in Reference Example 52 in place of Compound 1. Then, the resultant crude crystals were recrystallized from toluene/ethanol to give 1.22 g (yield 78%) of Compound 103 as a pale yellow powder.

Melting Point: 211.7-212.2°C

Elemental Analysis: $C_{19}H_{21}FN_4O_3 \cdot 0.25H_2O$			
Calcd. (%):	C, 60.55;	H, 5.75;	N, 14.87
Found (%):	C, 60.75;	H, 5.81;	N, 14.92

IR (KBr) ν_{max} (cm^{-1}): 1694, 1653, 1544, 1520, 1459

NMR (270MHz; DMSO-d_6) δ (ppm): 7.82(1H, dd, J=12.9, 2.0Hz), 7.59(1H, d, J=15.8Hz), 7.56-7.52(1H, m), 7.26(1H, d, J=15.8Hz), 7.19(1H, t, J=8.9Hz), 4.10-4.02(2H, m), 4.02(3H, s), 3.94-3.88(2H, m), 3.88 (3H, s), 1.25(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 54

(E)-8-(3-Chloro-4-fluorostyryl)-1,3-diethylxanthine (Compound 104)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-di thyluracil and 3.01 g (15.1 mmol) of 3-chloro-4-fluorocinnamic acid. Then, the resultant crude crystals were recrystallized from tetrahydrofuran/water to give 560 mg (yield 32%) of Compound 104 as a white powder.

Melting Point: >270°C

Elem ntal Analysis: $C_{17}H_{16}ClFN_4O_2$			
Calcd. (%):	C, 56.28;	H, 4.45;	N, 15.44
Found (%):	C, 56.30;	H, 4.43;	N, 15.53

IR (KBr) ν_{max} (cm^{-1}): 1695, 1649, 1504

NMR (270MHz; DMSO-d_6) δ (ppm): 7.93-7.91(1H, m), 7.66-7.63(1H, m), 7.58(1H, d, J=16.3Hz), 7.46(1H, t, J =8.9Hz), 7.08(1H, d, J=16.3Hz), 4.05(2H, q, J=7.1Hz), 3.93(2H, q, J=6.8Hz), 1.26(3H, t, J=7.1Hz), 1.14(3H, t, J=6.8Hz)

Reference Example 55

(E)-8-(3-Chloro-4-fluorostyryl)-1,3-diethyl-7-methylxanthine (Compound 105)

Substantially the same procedure as in Example 2 was repeated using 1.80 g (4.98 mmol) of Compound 104 obtained in Reference Example 54 in place of Compound 1. Then, the resultant crude crystals were recrystallized from ethyl acetate to give 820 mg (yield 44%) of Compound 105 as yellow needles.

Melting Point: 218.4-219.1°C

Elemental Analysis: $C_{18}H_{18}ClFN_4O_2$			
Calcd. (%):	C, 57.37;	H, 4.81;	N, 14.87
Found (%):	C, 57.23;	H, 4.85;	N, 14.81

IR (KBr) ν_{max} (cm^{-1}): 1693, 1648, 1541, 1505, 1438

NMR (270MHz; DMSO-d_6) δ (ppm): 8.18(1H, dd, J=7.2, 2.3Hz), 7.84-7.79(1H, m), 7.63(1H, d, J=15.8Hz), 7.51-7.44(2H, m), 4.11-3.99(2H, m), 4.05(3H, s), 3.92(2H, q, J=6.9Hz), 1.25(3H, t, J=6.9Hz), 1.13 (3H, t, J=6.9Hz)

Reference Example 56

(E)-1,3-Diethyl-8-(3-fluoro-2-methylstyryl)xanthine (Compound 108)

Substantially the same procedure as in Example 1 was repeated using 2.50 g (12.6 mmol) of 5,6-diamino-1,3-diethyluracil and 2.50 g (13.9 mmol) of 3-fluoro-2-methylcinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane to give 2.18 g (yield 51%) of Compound 108 as a white powder.

Melting Point: >270°C

Elemental Analysis: $C_{18}H_{19}FN_4O_2$			
Calcd. (%):	C, 63.15;	H, 5.59;	N, 16.36
Found (%):	C, 62.81;	H, 5.71;	N, 16.09

IR (KBr) ν_{max} (cm^{-1}) : 1696, 1658, 1499

NMR (270MHz; DMSO-d_6) δ (ppm): 13.7(1H, brs), 7.87(1H, d, J=16.6Hz), 7.59(1H, d, J=7.4Hz), 7.31-7.23(1H, m), 7.15(1H, t, J=8.7Hz), 7.05(1H, d, J=16.6Hz), 4.06(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 2.33 (3H, d, J=2.0Hz), 1.26(3H, t, J=7.1Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 57

(E)-1,3-Diethyl-8-(3-fluoro-2-methylstyryl)-7-methylxanthine (Compound 109)

Substantially the same procedure as in Example 2 was repeated using 1.30 g (3.80 mmol) of Compound 108 obtained in Reference Example 56 in place of Compound 1. Then, the resultant crude crystals were recrystallized from 2-propanol/water to give 1.12 g (yield 83%) of Compound 109 as white flocculent precipitates.

Melting Point: 198.1-198.7°C

Elemental Analysis: $C_{19}H_{21}FN_4O_2 \cdot 0.5H_2O$			
Calcd. (%):	C, 62.45;	H, 6.07;	N, 15.33
Found (%):	C, 62.39;	H, 6.26;	N, 15.25

IR (KBr) ν_{max} (cm^{-1}): 1695, 1654, 1543

NMR (270MHz; DMSO-d_6) δ (ppm): 7.85(1H, d, J=15.5Hz), 7.75(1H, d, J=7.9Hz), 7.34-7.27(1H, m), 7.29(1H, d, J=15.5Hz), 7.18(1H, t, J=8.9Hz), 4.12-4.04(2H, m), 4.04(3H, s), 3.92(2H, q, J=6.9Hz), 2.32(3H, d, J=1.7Hz), 1.27(3H, t, J=7.1Hz) , 1.13(3H, t, J=6.9Hz)

Reference Example 58

(E)-8-(3,4-Dihydroxystyryl)-1,3-diethyl-7-methylxanthine (Compound 110)

Compound 2 (2.00 g, 5.20 mmol) obtained in Example 2 was dissolved in 40 ml of methylene chloride. To the solution was added 26 ml (26 mmol) of boron tribromide (1.0M methylene chloride solution) under ice cooling in argon atmosphere, and the mixture was stirred overnight at room temperature. Methanol was added thereto and the mixture was separated with chloroform-an aqueous solution of sodium bicarbonate. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was recrystallized from ethanol to give 643 mg (yield 35%) of Compound 110 as pale yellow grains.

Melting Point: 247.5-248.2°C

MS-EI m/e: 356(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1675, 1642, 1543, 1520, 1298

NMR (270MHz; DMSO-d_6) δ (ppm): 9.31(1H, brs), 8.95(1H, brs), 7.50(1H, d, J=15.8Hz), 7.16(1H, s), 7.05(1H, d, J=7.9Hz), 7.00(1H, d, J=15.8Hz), 6.77(1H, d, J=7.9Hz), 4.06(2H, q, J=6.9Hz), 3.99(3H; s), 3.92 (2H, q, J=6.9Hz), 1.25(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 59

(E)-1,3-Diethyl-8-(3-hydroxy-4-methoxystyryl)-7-methylxanthine (Compound 111)

Compound 110 (400 mg, 1.12 mmol) obtained in Reference Example 58 was dissolved in 8 ml of dimethylformamide. To the solution were added 0.35 ml (5.62 mmol) of methyl iodide and 415 mg (5.62 mmol) of lithium carbonate, and the mixture was stirred at 80°C for 3.5 hours. Water was added thereto to dissolve lithium carbonate, followed by addition of chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform) to give 127 mg (yield 76%) of Compound 111 as a pale brown powder. The obtained crude crystals were further recrystallized from ethanol.

Melting Point: 204.5-205.8°C

MS-EI m/e: 370(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1689, 1653, 1515, 1442

NMR (270MHz; DMSO-d_6) δ (ppm): 9.06(1H, s), 7.53(1H, d, J=15.5Hz), 7.23(1H, s), 7.17(1H, d, J=8.3Hz), 7.08(1H, d, J=15.5Hz), 6.96(1H, d, J=8.3Hz), 4.06 (2H, q, J=6.9Hz), 4.00(3H, s), 3.92(2H, q, J=6.9Hz), 3.82(3H, s), 1.25(3H, t, J=6.9Hz), 1.13 (3H, t, J=6.9Hz)

Reference Example 60

(E)-1,3-Diethyl-8-(4-hydroxystyryl)-7-methylxanthine (Compound 112)

Compound 82 (2.70 g, 7.02 mmol) obtained in Reference Example 34 was dissolved in 50 ml of tetrahydrofuran. To the solution was added 17.6 ml of 2N hydrochloric acid, and the mixture was heated under reflux for 2.5 hours. The reaction solution was neutralized with a 2N aqueous solution of sodium hydroxide under ice cooling, water was added thereto, and the deposited crystals were collected by filtration. The obtained crude crystals were recrystallized from 2-propanol to give 2.33 g (yield 98%) of Compound 112 as yellow grains.

Melting Point: >270°C

Elem ntal Analysis: $C_{16}H_{20}N_4O_3$			
Calcd. (%):	C, 63.52;	H, 5.92;	N, 16.46
Found (%):	C, 63.17;	H, 6.02;	N, 16.18

IR (KBr) ν_{max} (cm^{-1}): 1696, 1636, 1607, 1517

NMR (270MHz; DMSO-d_6) δ (ppm): 9.79(1H, s), 7.62(2H, d, J=8.3Hz), 7.58(1H, d, J=15.8Hz), 7.08(1H, d, J=15.8Hz), 6.81(2H, d, J=8.3Hz), 4.07(2H, q, J=6.9Hz), 3.99(3H, s), 3.92 (2H, q, J=6.9Hz), 1.26 (3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 61

(E)-8-(4-Benzyloxystyryl)-1,3-diethyl-7-methylxanthine (Compound 113)

Compound 112 (100 mg, 0.29 mmol) obtained in Reference Example 60 was dissolved in 2 ml of dimethylformamide. To the solution were added 162 mg (1.17 mmol) of potassium carbonate and 0.28 ml (2.35 mmol) of benzyl bromide, and the mixture was stirred at 80°C for 2.5 hours. Water was added thereto under ice cooling to dissolve potassium carbonate and the deposited crystals were collected by filtration. The collected crude crystals were dissolved in chloroform, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was recrystallized from hexane/ethyl acetate to give 67 mg (yield 53%) of Compound 113 as yellow needles.

Melting Point: 184.7-185.4°C

Elemental Analysis: $C_{25}H_{26}N_4O_3$			
Calcd. (%):	C, 69.75;	H, 6.08;	N, 13.01
Found (%):	C, 69.70;	H, 6.26;	N, 12.79

IR (KBr) ν_{max} (cm^{-1}): 1688, 1655, 1513, 1245

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.53(2H, d, J=8.9Hz), 7.47-7.32(5H, m), 7.01(2H, d, J=8.9Hz), 6.78(1H, d, J=15.8Hz), 5.11(2H, s), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04 (3H, s), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 62

(E)-8-[4-(4-Bromobutoxy)styryl]-1,3-diethyl-7-methylxanthine (Compound 114)

Compound 112 (200 mg, 0.59 mmol) obtained in Reference Example 60 was dissolved in 4 ml of dimethylformamide. To the solution were added 163 mg (1.18 mmol) of potassium carbonate and 0.56 ml (1.18 mmol) of 1,4-dibromobutane, and the mixture was stirred at 50°C for 4 hours. Water was added thereto under ice cooling to dissolve potassium carbonate and the deposited crystals were collected by filtration. The obtained crude crystals were recrystallized from hexane/ethyl acetate to give 170 mg (yield 61%) of Compound 114 as pale yellow grains.

Melting Point: 174.8-176.4°C

Elemental Analysis: $C_{22}H_{27}BrN_4O_3$			
Calcd. (%):	C, 55.59;	H, 5.72;	N, 11.79
Found (%):	C, 55.68;	H, 5.85;	N, 11.69

IR (KBr) ν_{max} (cm^{-1}): 1688, 1656, 1515, 1244

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.53(2H, d, J=8.9Hz), 6.92(2H, d, J=8.9Hz), 6.77 (1H, d, J=15.8Hz), 4.21(2H, q, J=6.9Hz), 4.13-4.02 (4H, m), 4.04(3H, s), 3.50(2H, t, J=6.6Hz), 2.14-1.93(4H, m), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 63

(E)-8-[4-(4-Azidobutoxy)styryl]-1,3-diethyl-7-methylxanthine (Compound 115)

Compound 114 (235 mg, 0.49 mmol) obtained in Reference Example 62 was dissolved in 10 ml of dimethylformamide. To the solution was added 161 mg (2.48 mmol) of sodium azide, and the mixture was stirred at 80°C for 3 hours. Water was added thereto under ice cooling and the deposited crystals were collected by filtration. The collected crude crystals were dissolved in chloroform, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform), followed by recrystallization from hexane/ethyl acetate to give 216 mg (yield quant.) of Compound 115 as pale yellow grains.

Melting Point: 158.5-158.9°C

MS-EI m/e: 437(M^+)

Elemental Analysis: $C_{22}H_{27}N_7O_3$			
Calcd. (%):	C, 60.40;	H, 6.22;	N, 22.41
Found (%):	C, 60.15;	H, 6.31;	N, 22.32

IR (KBr) ν_{max} (cm^{-1}): 2094, 1653, 1605, 1543, 1515

NMR (270MHz; $CDCl_3$) δ (ppm): 7.75(1H, d, J=15.5Hz), 7.53(2H, d, J=8.6Hz), 6.92(2H, d, J=8.6Hz), 6.77 (1H, d, J=15.5Hz), 4.21(2H, q, J=6.9Hz), 4.13-3.69 (4H, m), 4.04(3H, s), 3.39(2H, t, J=6.6Hz), 1.93-1.79(4H, m), 1.38(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 64

(E)-8-[4-(4-Aminobutoxy)styryl]-1,3-diethyl-7-methylxanthine (Compound 116)

Compound 115 (75 mg, 0.17 mmol) obtained in Reference Example 63 was dissolved in 7.5 ml of tetrahydrofuran. To the solution was added 90 mg (0.34 mmol) of triphenylphosphine, and the mixture was heated under reflux for 3 hours. Water (5 ml) was added thereto and the mixture was heated under reflux for further one hour. After cooling, a 2N aqueous solution of sodium hydroxide was added thereto, and the mixture was extracted with chloroform and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol/triethylamine) to give 74 mg (yield quant.) of Compound 116. The obtained crude crystals were further recrystallized from 2-propanol/water.

Melting Point: 212.1-214.5°C

MS-EI m/e: 411(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1692, 1649, 1606, 1544, 1515

NMR (270MHz; DMSO-d_6) δ (ppm): 7.74(2H, d, J=8.6Hz), 7.62(1H, d, J=16.2Hz), 7.20(1H, d, J=16.2Hz), 6.98 (2H, d, J=8.6Hz), 4.08-3.88(6H, m), 4.02(3H, s), 2.83-2.74(2H, m), 1.82-1.59(4H, m), 1.26(3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 65

(E)-8-(4-Ethoxycarbonylmethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 117)

Compound 112 (300 mg, 0.88 mmol) obtained in Reference Example 60 was dissolved in 10 ml of dimethylformamide. To the solution were added 731 mg (5.29 mmol) of potassium carbonate and 0.47 ml (4.41 mmol) of ethyl chloroacetate, and the mixture was stirred at room temperature for 2 hours. Water was added thereto to dissolve potassium carbonate and the deposited crystals were collected by filtration. The collected crude crystals were dissolved in chloroform, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was recrystallized from hexane/ethyl acetate to give 341 mg (yield 91%) of Compound 117 as pale yellow needles.

Melting Point: 191.8-192.2°C

MS-EI m/e: 426(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1688, 1658, 1650, 1514, 1440

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.54(2H, d, J=8.6Hz), 6.94(2H, d, J=8.6Hz), 6.79 (1H, d, J=15.8Hz), 4.66(2H, s), 4.29(2H, q, J=6.9Hz), 4.21(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 1.38(3H, t, J=6.9Hz), 1.31 (3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 66

(E)-8-(4-Carboxymethoxystyryl)-1,3-diethyl-7-methylxanthine (Compound 118)

Compound 117 (200 mg, 0.47 mmol) obtained in Reference Example 65 was dissolved in a mixed solvent of 4 ml of tetrahydrofuran, 4 ml of ethanol, and 2 ml of water. To the solution was added 98 mg (2.34 mmol) of lithium hydroxide monohydrate, and the mixture was stirred at room temperature for one hour. To the reaction solution was added 2N hydrochloric acid, and the mixture was extracted with chloroform and dried over anhydrous sodium sulfate, followed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol/acetic acid) to give 40 mg (yield 21%) of Compound 118 as a pale yellow solid.

Melting Point: 267.5-269.0°C

MS-EI m/e: 398(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1684, 1653, 1647, 1515

NMR (270MHz; DMSO-d_6) δ (ppm): 7.74(2H, d, J=8.6Hz), 7.62(1H, d, J=15.8Hz), 7.20(1H, d, J=15.8Hz), 6.96 (2H, d, J=8.6Hz), 4.70(2H, s), 4.07(2H, q, J=6.9Hz), 4.01(3H, s), 3.92(2H, q, J=6.9Hz), 1.26 (3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Reference Example 67

(E)-1,3-Diethyl-8-(3-phenoxystyryl)xanthine (Compound 119)

Substantially the same procedure as in Example 1 was repeated using 3.00 g (15.1 mmol) of 5,6-diamino-1,3-diethyluracil and 4.00 g (16.7 mmol) of 3-phenoxycinnamic acid. Then, the resultant crude crystals were recrystallized from dioxane/water to give 3.82 g (yield 63%) of Compound 119 as pale yellow needles.

Melting Point: 241.4-243.4°C

Elemental Analysis: $C_{23}H_{22}N_4O_3$			
Calcd. (%):	C, 68.64;	H, 5.51;	N, 13.92
Found (%):	C, 68.26;	H, 5.59;	N, 13.79

IR (KBr) ν_{max} (cm^{-1}): 1640, 1579, 1492, 1265

NMR (270MHz; DMSO-d_6) δ (ppm): 13.52(1H, brs), 7.87 (1H, d, J=2.0Hz), 7.63(1H, dd, J=8.4, 2.0Hz), 7.56 (1H, d, J=16.3Hz), 7.16(1H, d, J=8.4Hz), 6.95(1H, d, J=16.3Hz), 4.06(2H, q, J=6.9Hz), 3.93(2H, q, J=6.9Hz), 3.89(3H, s), 1.26(3H, t, J=6.9Hz), 1.14 (3H, t, J=6.9Hz)

Reference Example 68

(E)-1,3-Diethyl-7-methyl-8-(3-phenoxystyryl)xanthine (Compound 120)

Substantially the same procedure as in Example 2 was repeated using 2.00 g (4.97 mmol) of Compound 119 obtained in Reference Example 67 in place of Compound 1. Then, the resultant crude crystals were recrystallized from hexane/ethyl acetate to give 1.78 g (yield 86%) of Compound 120 as yellow needles.

Melting Point: 205.1-205.9°C

Elemental Analysis: $C_{24}H_{24}N_4O_3$			
Calcd. (%):	C, 69.22;	H, 5.81;	N, 13.45
Found (%):	C, 69.02;	H, 5.80;	N, 13.48

IR (KBr) ν_{max} (cm^{-1}): 1692, 1652, 1492, 1241

NMR (270MHz; $CDCl_3$) δ (ppm): 7.74(1H, d, J=15.8Hz), 7.40-6.98(9H, m), 6.88(1H, d, J=15.8Hz), 4.20(2H, q, J=6.9Hz), 4.09(2H, q, J=6.9Hz), 4.04(3H, s), 1.37(3H, t, J=6.9Hz), 1.26(3H, t, J=6.9Hz)

Reference Example 69

(E)-1,3-Diethyl-8-(4-hydroxystyryl)xanthine (Compound 121)

Substantially the same procedure as in Reference Example 60 was repeated using 500 mg (7.02 mmol) of Compound 81 obtained in Reference Example 33. Then, the resultant crude crystals were recrystallized

from dioxane/water to give 430 mg (yield 98%) of Compound 121 as pale yellow needles.

Melting Point: >270°C

Elemental Analysis: $C_{17}H_{18}N_4O_3$			
Calcd. (%):	C, 62.57;	H, 5.56;	N, 17.17
Found (%):	C, 62.60;	H, 5.50;	N, 17.07

IR (KBr) ν_{max} (cm^{-1}): 1674, 1634, 1520, 1488

NMR (270MHz; DMSO-d_6) δ (ppm): 13.34(1H, brs), 9.77 (1H, s), 7.56(1H, d, J=16.2Hz), 7.46(2H, d, J=8.6Hz), 6.81(2H, d, J=8.6Hz), 6.80(1H, d, J=16.2Hz), 4.06(2H, q, J=6.9Hz), 3.94(2H, q, J=6.9Hz), 1.26(3H, t, J=6.9Hz), 1.14(3H, t, J=6.9Hz)

Reference Example 70

(E)-1,3-Diethyl-8-(4-hydroxy-2,3-dimethylstyryl)-7-methylxanthine (Compound 122)

Substantially the same procedure as in Reference Example 58 was repeated using 500 mg (1.31 mmol) of Compound 10 obtained in Example 10. Then, the resultant crude crystals were recrystallized from 2-propanol to give 290 mg (yield 60%) of Compound 122 as a pale yellow powder.

Melting Point: 240.2-242.0°C

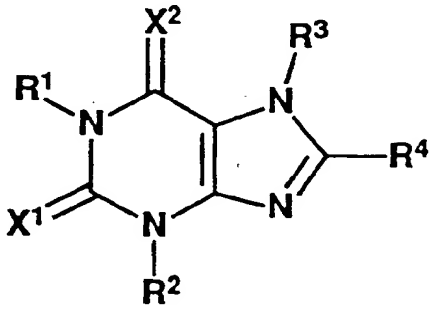
MS-EI m/e: 368(M^+)

IR (KBr) ν_{max} (cm^{-1}): 1683, 1656, 1586, 1460

NMR (270MHz; DMSO-d_6) δ (ppm): 10.20(1H, brs), 9.64 (1H, brs), 7.92(1H, d, J=15.6Hz), 7.57(1H, d, J=8.7Hz), 6.97(1H, d, J=15.6Hz), 6.74(1H, d, J=8.7Hz), 4.07(2H, q, J=6.9Hz), 3.99(3H, s), 3.91 (2H, q, J=6.9Hz), 2.29(3H, s), 2.10(3H, s), 1.26 (3H, t, J=6.9Hz), 1.13(3H, t, J=6.9Hz)

Claims

1. The use, in the manufacture of pharmaceutical compositions for use in the treatment of Parkinson's disease, of a xanthine derivative of Formula (I):



(I)

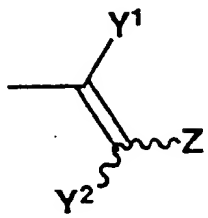
in which:

R^1 and R^2 each represent methyl or ethyl;

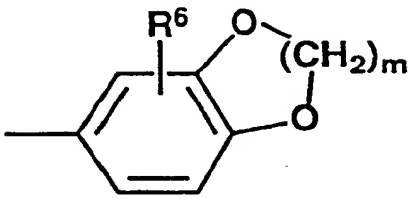
R^3 represents hydrogen, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl or alkynyl;

R^4 represents C_3-C_8 cycloalkyl; a -$(CH_2)_n$-R^5 group where n is 0 or an integer of from 1 to 4, and R^5 represents phenyl, naphthyl or a heterocyclic group or a substituted phenyl, naphthyl or heterocyclic group containing from 1-4 substituents selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, halogen, nitro, amino, mono- or di-(C_1-C_6) alkylamino, trifluoromethyl, benzyloxy, phenyl, phenoxy or C_1-C_6 alkoxy substituted by hydroxy, C_1-C_6 alkoxy, halogen, amino, azide, carboxy or (C_1-C_6 alkoxy)carbonyl;

or a



group where Y^1 and Y^2 each represent hydrogen, halogen, or C_1-C_6 straight or branched chain alkyl; and Z represents a



group in which R^6 represents hydrogen, hydroxy, C_1-C_6 straight or branched chain alkyl, C_1-C_6 straight or branched chain alkoxy, halogen, nitro, or amino, and m represents an integer of from 1 to 4; a phenyl, naphthyl or heterocyclic group or a substituted phenyl, naphthyl or heterocyclic group as defined under R^5;

and X^1 and X^2 each represent O or S;

or a pharmaceutically acceptable salt thereof.

2. The use according to claim 1 of a compound of Formula I, where X^1 and X^2 are both O, and Y^1 and Y^2 are both hydrogen.

3. The use according to claim 1 of a compound of Formula I, where X^1, X^2, Y^1 and Y^2 are as defined in claim 2, and where Z is phenyl, or phenyl containing from 1-4 substituents selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, halogen, nitro, amino, mono- or di-(C_1-C_6) alkylamino, trifluoromethyl, benzyloxy, phenyl, phenoxy or C_1-C_6 alkoxy substituted by hydroxy, C_1-C_6 alkoxy, halogen, amino, azide, carboxy or (C_1-C_6 alkoxy)carbonyl.

4. The use according to claim 1 of a compound as defined in claim 3, and where R^3 is a C_1-C_6 alkyl group.

5. The use according to claim 1 of a compound as defined in claim 3, and where R^3 is methyl.

6. The use according to claim 1 of a compound as required by claim 5, and wherein the group Z is phenyl containing from 1-4 C_1-C_6 alkyl or C_1-C_6 alkoxy substituents.

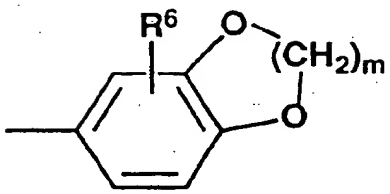
7. The use according to claim 1 of a compound as required by claim 6 and wherein the configuration at the position 8 of the xanthine ring is (E) form.

8. The use according to claim 1 of a compound as required by claim 7, wherein the said 1-4 substituents is or are methoxy or methyl groups.

9. The use according to claim 1 of a compound as required by claim 8 and wherein the R^1 and R^2 groups are both ethyl and the substituent(s) in the substituted phenyl group is or are 3,4-dimethoxy groups.

10. The use according to claim 1 of a compound as required by claim 7, wherein the said 1-4 substituents is or are thoxy or propoxy groups.

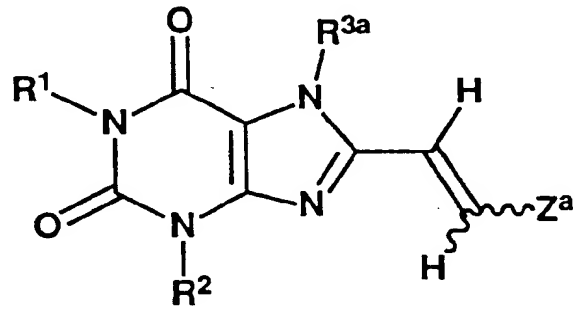
11. Th use according to claim 1 of a compound of formula I where X^1, X^2, Y^1 and Y^2 are as defined in claim 2 and where Z is



where R^3 is methyl; R^6 is hydrogen or methoxy; and m is 1 or 2.

12. The use according to claim 1 of a compound as defined in claim 11 in which R^1 and R^2 are ethyl; R^6 is 3-methoxy; and m is 1.

13. Xanthine derivatives of the formula (I-A):



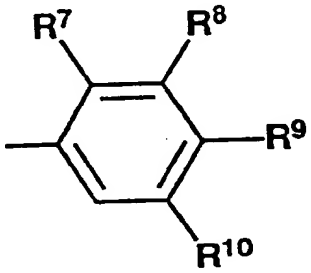
(I–A)

in which:

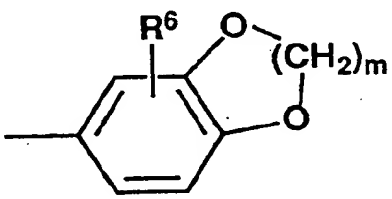
R^1 and R^2 are as defined in claim 1;

R^{3a} represents hydrogen or C_1-C_6 straight or branched chain alkyl; and

Z^a represents a



group wherein at least one of R^7, R^8 and R^9 groups is a C_1-C_6 straight or branched chain alkyl or alkoxy group and the others represent a C_1-C_6 straight or branched chain alkyl group or hydrogen; and R^{10} represents hydrogen or lower alkyl; or a

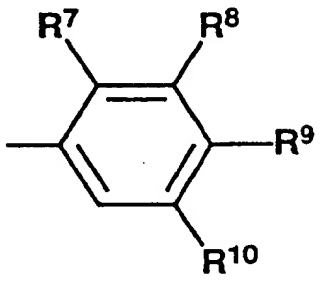


group wherein R^6 and m are as defined in claim 1;

and their pharmaceutically acceptabl salts.

14. A xanthine derivative according to claim 13, in which the configuration at the position 8 of the xanthine ring is (E) form.

15. A xanthine derivative according to claim 14, in which Z^a is a



group where R^7, R^8, R^9 and R^{10} are as defined in claim 13.

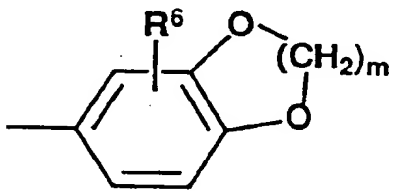
16. A xanthine derivative according to claim 15, in which R^{3a} is C_1-C_6 straight or branched chain alkyl.

17. A xanthine derivative according to claim 16, in which R^{3a} is methyl.

18. A xanthine derivative according to claim 17, in which one of R^7, R^8 and R^9 represents methyl, methoxy, ethoxy or propoxy and the others represent hydrogen; and R^{10} represents hydrogen or methyl.

19. A xanthine derivative according to claim 18, in which R^1 and R^2 are ethyl; R^8 and R^9 are methoxy; and R^7 and R^{10} are hydrogen.

20. A xanthine derivative according to claim 14, in which Z^a is a



group wherein R^{3a} is methyl; R^6 is hydrogen or methoxy; and m is 21 or 2.

21. A xanthine derivative according to claim 20, in which R^1 and R^2 are ethyl; R^6 is 3-methoxy; and m is 1.

22. A pharmaceutical composition containing a compound or salt as claimed in any one of claims 13 to 21 in admixture with a pharmaceutically acceptable carrier or diluent.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 7654
PAGE1

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X,P	CHEMICAL ABSTRACTS, vol. 118, no. 25, 1993, Columbus, Ohio, US; abstract no. 254617s, * abstract * & J. MED. CHEM. vol. 36, no. 10, 1993, WASHINGTON US pages 1333 - 1342 K.A. JACOBSON ET AL. & CAS REGISTRY 1993 (STN DATABASE) * Registry Numbers : 147700-33-2; 147700-21-8; 147700-19-4; 147700-17-2; 147700-13-8; 147699-98-7; 147699-95-4 *	1,13	C07D473/06 C07D473/08 C07D473/12 A61K31/52
Y D	CH-A-512 486 (PARKE, DAVIS AND COMPANY) * column 2-3; examples 2-4 * & US-A-3 641 010	1,13	
Y,D	WO-A-9 206 976 (KYOWA HAKKO KOGYO CO. LTD.) * examples 3,11,12 *	1,13	
X	WO-A-8 602 551 (THE UNITED STATES DEPARTMENT OF COMMERCE) * example 3; compound 1a *	1	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07D A61K
X	GB-A-2 135 311 (JOHN HOPKINS UNIVERSITY) * pages 3, 7-9; tables *	1	
X	EP-A-0 415 456 (KYOWA HAKKO KOGYO CO. LTD.) * example 12 *	1	
X	EP-A-0 374 808 (BOEHRINGER INGELHEIM K.G.) * examples 2,8,15,16; table I *	1	
X	EP-A-0 267 607 (MARION LABORATORIES INC.) * examples 1,6,14,20 *	1	

-/--

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	20 DECEMBER 1993	FRELON D.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 30 7654

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	US-A-4 755 517 (R.F. BRUNS ET AL.) * example 4 *	1	
Y,D	J. MED. CHEM. vol. 34, no. 4, 1991, WASHINGTON US pages 1431 - 1435 R.H. ERICKSON ET AL. * examples 16a-20; table II *	1	
Y	US-A-4 968 672 (K.A. JACOBSON ET AL.) * column 10 *	1	
A	EP-A-0 203 721 (THE WELLCOME FOUNDATION) * examples 1,4,20,21 *	1	
A	EP-A-0 092 398 (WARNER-LAMBERT COMPANY) * page 1 *	1	
A,P	DATABASE WPI Week 9303, Derwent Publications Ltd., London, GB; AN 93-021440 & JP-A-4 346 986 (KYOWA HAKKO KOGYO K.K.) * abstract *	1	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A	EP-A-0 470 317 (ADIR ET COMPAGNIE) * abstract *	1	
A	EP-A-0 215 736 (SANDOZ A.G.) * examples 11-13, 19, 26-28, 32 *	1	
A D	EP-A-0 103 497 (ADIR) * abstract * & JP-A-59 042 383 (ADIR)	1	
A	FR-A-2 514 003 (INVESTIGACION TECNICA Y APLICADA) * the whole document *	1	

-/--

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	20 DECEMBER 1993	FRELON D.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 7654
PAGE3

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	US-A-3 624 215 (H.H. STEIN ET AL.) * column 1 - column 2 *	1	
A	US-A-3 624 216 (H.H. STEIN ET AL.) * column 2 *	1	
A	US-A-3 900 474 (R.D. GINGER ET AL.) * example 8 *	1	
A	US-A-2 729 642 (R.M. BURGISON) * example *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	20 DECEMBER 1993	FRELON D.

EPO FORM 1503 03.82 (P0401)

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document